DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1976

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HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES

NINETY-FOURTH CONGRESS

FIRST SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE

DANIEL J. FLOOD, Pennsylvania, *Chairman*

WILLIAM H. NATCHER, Kentucky
NEAL SMITH, Iowa
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PART 3

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

Printed for the use of the Committee on Appropriations

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DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR FISCAL YEAR 1976

WEDNESDAY, APRIL 9, 1975.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH

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CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. Now we have the National Institutes of Health.

The presentation will be made by Dr. Ronald W. Lamont-Havers, Acting Director, National Institutes of Health.

I see we have a biographical sketch of you, Doctor, which will be placed in the record at this point.

[The biographical sketch follows:]

BIOGRAPHICAL SKETCH OF RONALD WILLIAM LAMONT-HAVERS, M.D.

Name: Ronald William Lamont-Havers, M.D.
Position: Acting Director, National Institutes of Health.
Birthplace and date: Wymondham, Norfolk, England, March 6, 1920.
Education: B.A., University of British Columbia, Canada 1942; M.D., University of Toronto, Canada 1946; Diploma Internal Medicine, McGill University, Montreal, Canada 1953.

EXPERIENCE

January 1975 to present, Acting Director, National Institutes of Health, Bethesda, Md.
August 1974 to present, Deputy Director, National Institutes of Health, Bethesda, Md.

May 1974 to August 1974, Acting Deputy Director, National Institutes of Health.

August 1972 to May 1974, Deputy Director, National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH.

1973, U.S. Coordinator, U.S.-U.S.S.R. Cooperative Program in Arthritis.

1973, Chairman, DHEW Study Group on the Protection of Human Subjects in Biomedical and Behavioral Research.

1968–72, Associate Director fof Extramural Research and Training, National Institutes of Health.

1964–68, Associate Director for Extramural Programs, National Institute of Arthritis and Metabolic Diseases, NIH.

1965, consultant, Grayson Foundation, Inc., Lexington, Ky.

1964–66, editor, Bulletin on Rheumatic Diseases.

1964, member, official delegation to U.S.S.R. re arthritis exchange program.

1955–64, instructor in medicine, College of Physicians and Surgeons, Columbia University, New York, N.Y.

1962, consultant, code authority of the National Association of Broadcasters.

1955–64, medical director, the Arthritis Foundation, New York, N.Y.

1953–55, medical director, Canadian Arthritis and Rheumatism Society, British Columbia Division, Vancouver, B.C., Canada (also private practice and consulting positions).

1951–53, fellow of the Canadian Arthritis and Rheumatism Society, College of Physicians and Surgeons, Columbia University, New York, N.Y.

1949–51, Queen Mary Veterans Hospital, Montreal, P.Q., Canada; residency—internal medicine.

1946–48, Vancouver General Hospital, Canada—House staff and residency training.

1944–46, Royal Canadian Army Medical Corps.

PROFESSIONAL AND SCIENTIFIC MEMBERSHIPS

Arthritis Foundation (board of directors and governing member, 1966 to present, medical advisory committee 1971); Dermatology Foundation (medical advisory committee and executive committee, 1967 to present); American Rheumatism Association; New York Rheumatism Association (president 1960); Canadian Rheumatism Societies; American Rheumatism Association of Metropolitan Washington (board of directors, 1964 to present; medical advisory committee, 1969 to present); D.C. Rheumatism Society (president 1971); affiliate member, American Gastroenterological Association; Fellow, Royal College of Physicians (Canada)—internal medicine 1952.

HONORS

1946, Alpha Omega Alpha; Superior Service award, Department of Health, Education, and Welfare, 1973; Golden Pen award, editorial board, Journal of the American Physical Therapy Association, 1965.

Mr. FLOOD. Do you have some people with you that you want us to meet?

Dr. LAMONT-HAVERS. Yes, sir. I would like you to meet Dr. DeWitt Stetten on my right, the Deputy Director for Science at NIH. I believe Dr. Stetten appeared before you last year.

Mr. FLOOD. Yes; he has been around.

Dr. LAMONT-HAVERS. And Mr. Leon Schwartz, the Associate Director for Administration.

As backup witnesses I have Dr. Thomas Malone, Associate Director for Extramural Research and Training, and Mr. Bruce Carson, the Acting Associate Director for Program Planning, and Mr. Norman Mansfield, Director of the Financial Management at NIH, and, of course, at the table we also have Mr. Charles Miller, whom I believe you know.

Mr. FLOOD. All right, I see you have a prepared statement, Doctor.

What do you want to do with it?

Dr. LAMONT-HAVERS. I should like to read it, Mr. Chairman.

Mr. FLOOD. Whatever you want.

Dr. LAMONT-HAVERS. Mr. Chairman and member of the committee. As the Directors of the major components of the National Institutes of Health—the 11 research institutes, the Division of Research Resources, the Fogarty International Center and the National Library of Medicine—will discuss their respective activities and testify in support of the separate appropriation requests, I should like to precede my general testimony on the NIH budget with a brief discussion of several matters, affecting the whole of NIH, that are of concern not only to members of this committee but to a number of other Members of the Congress.

DISSEMINATION OF RESEARCH RESULTS

One of these items is the problem of the dissemination of the results of research—both that conducted at NIH and that conducted at other institutions. The rapid increase, during the past 20 years, in the amount of effort put into biomedical research—whether measured in terms of manpower, facilities or funds—and the astonishingly broadened scope of the work being done has led to an avalanche of papers and reports—and a burgeoning of journals in which to print them—that does, indeed, appear to be overwhelming and undigestible.

It is probably true that there are more people actively engaged in biomedical research today than the total of all people so engaged from the beginning of civilized society to the beginning of World War II. In the United States alone, identifiable support for medical research and development, from all sources, has grown from less than $100 million in 1947 to more than $4 billion today. The pattern in a number of other countries is similar though, perhaps, somewhat less dramatic. It is therefore quite understandable that fears should, from time to time, be expressed that the inability of an individual scientist or even of a large research team to keep abreast of more than a small fraction of the large mass of new information now being produced may result, at best, in unnecessary duplication—doing work that has already been done—and, at worst, in a failure to apply already available knowledge to the treatment of patients. This latter concern appears in its most excited form in the allegation that the cure for cancer lies buried on some library shelf.

At the direction of this committee's counterpart in the Senate, we have taken a hard look at the problem of information dissemination and have prepared an action report with recommendations and a plan for implementation which were requested. Mr. Chairman, I should like to submit copies of this report and of the plan of action, based on its recommendations, for the information of this committee, if you should so wish.

Mr. FLOOD. Yes; we do.

Dr. LAMONT-HAVERS. The ad hoc group of senior scientists, administrators and communication experts, who reviewed the present practices and shortcomings in the dissemination of research findings by NIH, emphasized that three quite separate sets of communication linkages are involved:

First, from scientist to other scientists;

Second, from scientist to practicing health professionals; and

Third, from scientist to the public which also has need of relevant healthcare information.

Not only are the channels for communication to these three groups of recipients very different, but the kind of research findings needed by or useful to each group must be carefully identified.

Due to the complexity of biomedical problems, the vast majority of research findings are of a type that might be compared to the placement of a single piece into a large and very difficult jigsaw puzzle. Such a finding has no meaning for the general public and is of no use to the physician, or other health-care practitioner, who—if I may pursue the analogy—can only derive usable information from a completed, or virtually completed, picture. I have no data on which to base an estimate of the proportion of research findings that fall into the category of being of interest only to other scientists working in the same, or a closely related, field, but something like 80 percent would, I think, be an appropriate impressionistic figure. The channels for communicating these highly technical and often rather abstruse findings are well established and well worn by constant and effective use. In addition to the traditional devices, such as journal publication and scientific meetings, they now include elaborate systems for the storage, retrieval, and distribution of information by computer and a criss-cross network of direct personal communication to whose rapidity and efficiency most scientists will readily attest.

I might add, Mr. Chairman, that our National Library of Medicine has been most effective in increasing and helping this aspect.

There is certainly room for improvement, particularly in the continued application of computer technology to information collation and retrieval, but no fundamental changes in the scientist-to-scientist communication system seem to be necessary or desirable—or, for that matter, desired by those most directly involved.

There is a second category of research findings which clearly point to potential application in the prevention, diagnosis, or treatment of disease, but which require further development or refinement before they can become part of the practicing physician's armamentarium. This group—to which I would assign an impressionistic figure of, say, 15 percent of all research findings—includes drugs and procedures that have proved effective in animals or in a few experimental human cases but clearly require carefully monitored clinical trials before being judged both safe and effective: it includes biologicals and pharmaceuticals that have been produced in the laboratory but for which suitable methods for commercial production in adequate quantities must still be developed; it includes procedures that because of the complex techniques or highly specialized and expensive equipment required cannot yet be made generally available; it, regrettably, also includes drugs and devices that are very expensive to produce but for which the potential demand is so small—perhaps because of the rareness of the diseases for which they are designed—that no manufacturer will undertake their production. For this category of research findings, the problem is not simply a question of communication but of arranging for the clinical trials, the development of production methods, the instruction in complex new techniques, or the financing of manufacture, or of overcoming whatever other factors—such as Federal patent policy—stand in the way of widespread application to patient care. The solution in these cases must be tailored to the problems at hand, and the solution does not always lie within the scope of NIH's mission or authority.

There remains, however, a category of research findings—say 5 percent of the total—that are of immediate importance to practitioners, and it is quite clear that present methods of dissemination, whatever their theoretical merits, are not doing the job adequately. The recommendations of the ad hoc review group include improvements or expansion of existing communication methods and the exploration of a number of new approaches, such as the establishment of regional information centers to provide comprehensive telephonic consultative service for practicing health professionals; the more extensive use of audiovisual and videotape materials; and the broadcasting of clinical conferences, seminars, and demonstrations via the new communications technology satellite that will be launched later this year. I must emphasize, however, that all efforts aimed at the continuing education of the physician and other health-care personnel must depend for their success on the receptiveness of these practitioners. Most doctors, for example, are very busy, and too many of them are content to rely on the knowledge they have acquired in medical school, from their subsecquent experience, and from the pharmaceutical "detail men" who periodically call on them. Even among those who are keenly aware of the need to keep up with new developments, many are diverted by genuine lack of time or by the competition of other interests and community commitments. There can thus be no certain method for bridging the gap between knowledge at the research frontier and knowledge at the bedside.

REGIONAL MEDICAL PROGRAMS

Mr. FLOOD. That is interesting. You know about the regional medical program.

Dr. LAMONT-HAVERS. Yes, sir.

Mr. FLOOD. It was the intent and purpose of the regional medical programs to do just exactly what you are talking about. Here we have all this information, all this potential, and it goes without merit or value unless, as you were just saying, it is delivered in proper form and made available to the practitioner, and the bridge between those two elements was to be the regional medical programs.

Dr. LAMONT-HAVERS. That is right.

Mr. FLOOD. That being the case, I wonder why this interest downtown in doing away with the regional medical programs in the classical Washington tradition.

Dr. LAMONT-HAVERS. Fortunately, Mr. Chairman, doing away with the RMP is not the responsibility of NIH.

Mr. FLOOD. I know, but there you are. You happen to be sitting there.

Dr. LAMONT-HAVERS. The problem which was tackled by the regional medical program was important, but it is my impression that it is expected that the mission of RMP would be encompassed in new types of programs which are being developed.

Mr. MILLER. Mr. Chairman, one word though. I need to expand on that.

Your phrase "interest downtown," as you know, the legislation itself ultimately phases out the RMP's. I think the issue is how fast but not whether.

Mr. FLOOD. Oh, yes, I know that. We know a great deal about abortions down here. You know where the baby was born though, don't you?

Go ahead.

Dr. LAMONT-HAVERS. There is no guarantee that audiovisual materials will be used, that satellite broadcasts will be heard, or that telephonic consultations will take place as often as may be desirable.

NIH is ready to embark on a program, in cooperation with other agencies of the Public Health Service and elsewhere, to take all reasonable and feasible steps, within the limitation of resources, to make usable information as easily and readily available as possible. We shall do all we can to make sure that if the horse doesn't drink it will not be because he was not led to water.

Public interest in research information has three aspects: As taxpayers, people want and have a right to know what NIH is doing with its not inconsiderable budget and how well its mission is being carried out; as intelligent citizens, people have a keen interest in research progress in a field that directly affects their health and happiness; and as concerned individuals, they need to be informed about health practices that will prevent disease which they can apply on their own initiative and about available diagnostic and therapeutic measures for which they should seek professional help. To this end, NIH will continue such large-scale efforts as the national high blood pressure educational program and the national sickle cell disease program and will expand, as necessary, its activities for providing substantive information on disease questions through the press, the broadcast media, and in response to direct inquiries of which NIH received more than 800,000 last year. More general participation in the dissemination of health information will be in cooperation with the new Bureau of Health Education, in the Center for Disease Control, which is responsible for coordinating such efforts.

PRIMITIVE STATE OF BIOLOGICAL RESEARCH

The categorization of research findings according to their immediate relevance to medical practitioners illustrates the importance of what is sometimes rather misleadingly referred to as basic research. Although I would emphasize that the impressionistic figures I used should not be taken too literally, the bulk of the work with which biomedical research is most deeply concerned stands necessarily at some distance from immediate application. I say "necessarily" because the biological sciences differ from the physical sciences—physics, chemistry, metallurgy, astronomy, even meteorology—in being in a much more primitive state. In each of the physical sciences, the basic principles are, for the most part, well understood and there are precise and mathematically usable "laws" that lend themselves to extensive predictive use—indeed, the whole technology of engineering is based on these laws. Biology has, as yet, no counterpart for the laws of thermodynamics or Mendeleev's periodic table which brought order and predictability into inorganic chemistry—and there is certainly nothing to compare to the simplicity and devastating applicability of Einstein's $E=MC^2$. Biological research is still largely empirical and much of the technology of medicine is based on the application of and extrapolation from observations whose real bases and significance are, at best, only par-

tially understood and are often not understood at all. In terms of the jig-saw puzzle analogy, medical researchers do not know whether the blue piece they have found is part of the sky, the lake in the background, the evening dress of the girl on the porch, or the body of the stationwagon in the driveway. And sometimes they manage to fit it very convincingly into what later turns out to be the wrong place. Rapid progress in medical research can only be expected when the basic principles of some area of inquiry are more or less clearly understood. For example, when it was discovered, in the late 1800's, that bacteria were a cause of diseases and when "Koch's postulates" for establishing the bacterial cause of a particular disease had been worked out, there was dramatic progress in the prevention and treatment of a whole group of infectious diseases before which the physician had theretofore been powerless.

I might add, Mr. Chairman, that Koch's postulates, which stood us in good stead in the bacterial age, are of very little value in, say, the discovery of a human cancer virus. You can't take such a virus and put it back into a human to make sure that it does cause cancer. So we have great practical problems in applying such a well-established procedure as that outlined by Koch.

IMPORTANCE OF FUNDAMENTAL RESEARCH

I am confident that the work being done now in such fields as the molecular biology of the cell and on those mechanisms for the transmission of genetic information—all of which is still esoteric and far removed from any practical application to the treatment of disease—will eventually fall into place in a coherent picture. It may well provide the answer to a host of disease problems and once more revolutionize the practice of medicine, as the advent of bacteriology did at the beginning of the century. Research into the fundamentals of biological processes—which, in that sense, may well be called basic research—is a long-term but also a most profitable investment which must retain its prominent place in the NIH portfolio. Research aimed at the elucidation of basic principles has the highest cost-effectiveness—especially in contrast to clinical trials which are very expensive and whose main purpose is usually merely to confirm laboratory results—and it is not too much to say that achieving better health for future generations of Americans will depend directly on the success of such fundamental research efforts.

FORCES DETERMINING NIH'S ROLE

The question of program balance obviously comes to the fore when economic conditions result in some tightening of available funds. The allocation of funds to various activities within the NIH mission has, in the past, been the resultant of three sets of forces. The first determinant has been societal disiderata, as expressed through the political process. This was evident in the early history of NIH with the creation of the National Cancer Institute as the first of the categorical institutes, and in the subsequent addition, one by one, of other disease-oriented institutes. These societal pressures have resulted, more recently, in the special legislation and increased funding for cancer research and heart and lung research; in the creation of the Eye, En-

vironmental Health, and Aging Institutes—but, I might add, not necessarily with the addition of resources—and in special emphasis for digestive diseases.

The second determinant has been decisions at various levels within the administration—OMB——

Mr. PATTEN. Or should that be first?

Dr. LAMONT-HAVERS. No.

Mr. PATTEN. Have you got your priorities wrong?

Dr. LAMONT-HAVERS. No, Mr. Patten. I do feel that the societal pressures are the most important.

—The Office of the Secretary, and at NIH itself—on the relative emphasis to be given, in terms of the distribution of funds and personnel, to the several Institutes and to programs within each Institute—how much for grants, how much for contracts, how much for training—to conform to a proper role for the Federal Government and to carry out the mission of NIH. The third determinant has been the scientific community's perception of opportunities for productive research, as reflected in the nature of research grant applications, and its assessment of the relative merit and importance of these opportunities, as reflected in peer review system's assignment of priorities which, in effect, decide which projects will be funded and which will not. The interaction of these three determinants inevitably creates some frictions but I believe that NIH, as an institution, has grown and prospered and that its programs have attained a high degree of success because its course has been jointly directed by public demand, national policy, and scientific feasibility. These counterbalancing forces will be equally effective in determining the role that NIH should play, during the next decade, in relation to the Federal Government's increasing involvement in the delivery of health services. The importance of research to the ability of the medical profession to cope with the Nation's health problems and the decisive role which NIH could play in upgrading the quality of medical care available throughout the country would have a significant impact on the national health program.

At the same time, the diversion of NIH from its primary task of producing new knowledge in order to give it a more direct role in national health service programs might well have the unproductive effect of converting a unique first-class research institution into a third-rate service appendage. The whole question of the proper role for NIH, in the light of the changing national health picture, is not only being examined by NIH itself but is also under review by the President's Biomedical Research Panel whose observations and recommendations will, no doubt, stimulate further debate on the proper future scope of NIH's mission.

VALUE OF INTRAMURAL RESEARCH

Another aspect of the role of NIH about which conflicting views have been expressed is the future of its intramural research program. In this case, however, the alternatives seem to me to be very much clearer. Historically, NIH is a Federal research laboratory which, when it was 50 years old (in 1937), began to make a few research grants, under the aegis of the newly created Cancer Institute; at the end of World War II, it inherited the medical research grant program of the

Office of Scientific Research and Development. Today the extramural programs clearly overshadow the intramural program in the budget—and in the eyes of NIH grantees—but in terms of personnel, facilities and international prestige NIH remains predominantly an intramural research institution. Only 10 percent of the NIH budget is earmarked for its laboratories and clinics but 75 percent of its staff is engaged in research and its ancillary services. Most of the buildings on the NIH campus at Bethesda are devoted to in-house research (some 1.3 million square feet) as are all of the facilities at the animal farm in Poolesville, the geriatric research center in Baltimore, the cancer installation at Fort Detrick, the Rocky Mountain Laboratory, the Indian research center in Phoenix—and, of great importance, the National Institute of Environmental Health Sciences in North Carolina. NIH is the largest biomedical research institution in the world and it is certainly also considered one of the most prestigious. Its standing is attested by the number of honors and awards its staff has received—including 3 Nobel Prizes to scientists working at NIH and 2 Nobel Prizes to scientists at other institutions for work they started while on the NIH staff. The esteem and affection in which NIH is held by its alumni is illustrated by their spontaneous proposal and active promotion of a reunion at NIH later this month as part of the Bicentennial observation.

It is now being said in some academic circles that, in present circumstances, with a flourishing biomedical research community throughout the country, there is no need for direct Federal participation in the conduct of biomedical research—that, with appropriate Federal support, the non-Federal establishment could do it all. A strong rebuttal can be made to this proposition, but the argument would be relevant only if it were now being proposed to create a Federal research institute *ab initio*. There is certainly no valid reason for dismantling a large, prestigious and productive organization that already exists and has a very substantial investment in specialized facilities and highly trained permanent staff. Moreover, the contribution made by intramural research to the extramural programs, while difficult to document, is very real. Not only do the Institutes contain eminent and experienced scientists who are actively enaged at the forefront of research, on which the extramural staff can—and does—draw for substantive guidance and advice, but the status that extramural program managers enjoy in dealing with grantee institutions is due in large measure to the peer status accorded NIH as a research center in its own right.

TRAINING AND FELLOWSHIP PROGRAMS

The NIH training programs are, as you know, in a further stage of transition since the National Research Service Awards Act (Public Law 93–348) came into effect on July 12, 1974, superseding the program launched by Secretary Weinberger in July 1973 which, in turn, superseded the traditional—now called "old"—fellowship and training programs. The phase out period for the "old" fellowship program has been extended to 1979 by the new old-style awards made during 1974 with the court-ordered release of funds impounded in fiscal year 1973. The budget includes $633,000 for such fellowships in fiscal year

1976. The phaseout of the fellowships awarded under the Secretary's fiscal year 1974 guidelines, with a maximum 3-year commitment, will extend through fiscal year 1977 as a few awards were made that started in fiscal year 1975. The budget includes $14,518,000 for these fellowships. For the phaseout of the "old" training grants, the budget includes $71,788,000.

The budget request includes $36,707,000 for National Research Service Awards (including both fellowships and institutional awards) under the new act. No awards have yet been made under its authority. The proposed regulations, which were published, for comment, in the Federal Register on January 17 are now ready for publication in their final form. Over 3,000 applications have, however, already been reviewed of which somewhat less than half will be approved and awarded. Further applications are now being reviewed. The fiscal year 1975 appropriation includes $40,365,000 for this program. The major distinguishing feature of these grants, in contrast to the guidelines for the "old" and the current fellowships, is that for each year of support the recipient is expected to serve 1 year in a research or teaching post or serve in the National Health Service Corps or, under certain conditions, serve 20 months in another health-related activity. Awards will this year be made for both predoctoral and postdoctoral training and institutional awards. The budget proposal for fiscal year 1976 limits this program to postdoctoral training in areas of short supply.

One important requirement of the new act is that the National Academy of Sciences conduct a continuing study of the manpower needs of the various biomedical disciplines; the kind and extent of training which should be provided; and assess the adequacy or redundancy of training programs under the act. Awards can only be made in disciplines for which the Academy sees a need for additional personnel. The Academy has just completed a 3-month feasibility study and has agreed to undertake the required study and furnish preliminary data by the end of June.

THE BUDGET REQUEST IN PERSPECTIVE

You are already well aware of the circumstances under which the fiscal year 1976 budget requests for the National Institutes of Health were formulated. The estimates before you for the NIH programs for research on health also reflect the administration's overriding fiscal policy for restoring the Nation's economic health. The President's determination—which he reiterated when he signed the tax-cut bill—not to increase the projected budget deficit any further clearly imposes constraints on all controllable Federal expenditures and the support of biomedical research is no exception. I think it should be readily admitted that the maintenance of the existing NIH programs with the funds requested will present us with some awkward problems—it is a tight budget and it is certain to pinch in a number of places. But I am equally certain that biomedical research activities throughout the country would suffer far more if this country were caught up in an uncontrollable inflationary spiral or if it were plunged into a serious and protracted depression. I believe that a tight and

admittedly difficult budget is a small price to pay if it helps to avert these much more gruesome alternatives.

It was, as you know, the administration's intent to restrict NIH's fiscal year 1975 obligations to a little over $1.7 billion so that the fiscal year 1976 budget request for $1.8 billion would have given us an overall increase of about 4 percent and would thus have maintained the programs at a roughly constant level over the 2-year period. However, with the rejection of the President's rescission proposal, nearly $2.1 billion will, in fact, be available in new obligational authority this year and there will be a net overall reduction of not quite 14 percent in fiscal year 1976. We hope to so manage our affairs that the impact of this reduction in available funds will be minimized but some difficulties will be unavoidable. I should, however, like to put this situation into its proper perspective.

In the first place, $1.8 billion is an immense amount of money and to pretend that it is insufficient to sustain a very vigorous and wide-ranging research program, and its ancillary activities, would be disingenous. It will not be enough to permit us to support everything we would like to support and which we feel merits support—but, now that so large and flourishing a medical research establishment has been created in this country, this will always be the case. I fully concur in Dr. Stone's observation to this committee last year that no rational NIH budget will ever suffice to meet all demands or satisfy all worthy claimants for support.

When I came to NIH in December 1964 the comparable appropriation was $831 million. We are now asking for almost a billion dollars more than that. In fact, this so-called "hard times" budget is 50 percent greater than the appropriation of $1.2 billion just 5 years ago. Only a part of that large increase has been absorbed by inflation. In other words, I believe that the amount requested in the budget continues to represent a major investment in biomedical research on a scale that no other country even attempts and in a way that will enable us to maintain well-balanced program consistent with our present activities.

Mr. FLOOD. Thank you, Doctor.

The NIH budget for 1976 is $285 million below the 1975 appropriation. That is quite a chunk.

There is one statement that appears throughout your budget justification sheets. Let me quote that statement: "Low priority, noncompeting grants, will not be funded in 1976."

If these projects are of such low priority, why were they funded to begin with?

Dr. LAMONT-HAVERS. Mr. Chairman, I think as Dr. Cooper pointed out on Monday, low priority is a relative term.

Mr. FLOOD. Oh, yes, I know that. I thought you knew that.

Dr. LAMONT-HAVERS. Yes, sir. As a matter of fact, we would be most reluctant not to fund any of these noncompeting applications. Certainly the level of priorities at which we have been funding in the past few years has made support available on highly meritorious scientific endeavors. It is a matter then of relatively: whether one cuts off at a score of 150 or 140.

Mr. FLOOD. You use a half-dozen scientific references here all during your report. Relatively is another one.

Dr. LAMONT-HAVERS. That is right.

Mr. FLOOD. What is it? Are you simply running out of these good, high quality extramural works to support over there at NIH? Is that why each institute is identifying a sizable number of what you call low priority projects that you are not going to fund in 1976?

Dr. LAMONT-HAVERS. I think, Mr. Chairman, that the term "low" should either have been "lower" or some adjective other than "low."

Mr. FLOOD. There is the totem pole now. Where are you? Is it that kind of thing?

Dr. LAMONT-HAVERS. That is right, it depends on where you cut off on the totem pole.

RESEARCH GRANTS

Mr. FLOOD. Let me ask you this: How many new research grants will NIH be able to award under this budget?

Dr. LAMONT-HAVERS. It depends, Mr. Chairman, on what is indeed determined. As has been indicated in the testimony, how we actually utilize the 1976 budget has not been quite determined. If, indeed, we utilize the funds available to us in fiscal year 1976 primarily to pay the commitments which we have already incurred, then we could utilize practically all of that money set aside for new or competing applications to pay our commitments.

Mr. FLOOD. How?

Dr. LAMONT-HAVERS. In which case we would not fund any new projects.

Mr. FLOOD. How many new research grants do you normally fund each year?

Dr. LAMONT-HAVERS. We normally fund approximately 4,000 new grants each year.

Mr. FLOOD. Do this for the record, provide for the record a table which lists by institute and by number of grants, with of course the appropriate dollar amounts awarded in 1975 as either noncompeting or competing. That is projects. Then show how many of these grants will be carried over in fiscal 1976 with the commitment for additional funding.

You had better work with the staff of the committee on that too. That can be a can of worms.

Dr. LAMONT-HAVERS. Yes.

The information follows:

National Institutes of Health

1976 GRANT AND CONTRACT COMMITMENTS
(Dollars in thousands)

	1975 Comparable		1976 Commitments		1976 Budget Request		Difference	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
CANCER								
Research Grants:								
Noncompeting.....	1376	$161,027	1864	$217,831	1401	$164,286	-463	-$53,545
Competing.....	1146	113,572						
Contracts:								
Noncompeting.....	790	180,162	795	181,157	715	163,056	-80	-18,101
Competing.....	88	20,012						
Total:								
Noncompeting.....	2166	341,189	2659	398,988	2116	327,342	-543	-71,646
Competing.....	1234	133,584						
HEART								
Research Grants:								
Noncompeting.....	1129	126,661	1253	148,047	1008	129,000	-245	-19,047
Competing.....	436	54,068						
Contracts:								
Noncompeting.....	250	55,811	330	80,000	290	63,828	-40	-16,172
Competing.....	100	24,717						
Total:								
Noncompeting.....	1379	182,472	1583	228,047	1298	192,828	-285	-35,219
Competing.....	536	78,785						
DENTAL								
Research Grants:								
Noncompeting.....	200	17,547	302	24,281	203	18,249	-99	-6,032
Competing.....	156	8,701						
Contracts:								
Noncompeting.....	42	3,321	57	4,908	51	4,171	-6	-737
Competing.....	18	1,500						
Total:								
Noncompeting.....	242	20,868	359	29,189	254	22,420	-105	-6,769
Competing.....	174	10,201						
ARTHRITIS								
Research Grants:								
Noncompeting.....	1323	79,773	1591	108,461	1198	86,999	-393	-21,462
Competing.....	709	43,464						
Contracts:								
Noncompeting.....	69	5,629	81	6,585	69	5,650	-12	-935
Competing.....	22	1,776						
Total:								
Noncompeting.....	1392	85,402	1672	115,046	1267	92,649	-405	-22,397
Competing.....	731	45,240						
NEUROLOGY								
Research Grants:								
Noncompeting.....	769	55,062	1070	71,995	712	54,414	-358	-17,581
Competing.....	584	33,808						
Contracts:								
Noncompeting.....	53	6,682	73	9,289	55	7,028	-18	-2,261
Competing.....	28	3,378						
Total:								
Noncompeting.....	822	61,744	1143	81,284	767	61,442	-376	-19,842
Competing.....	612	37,186						
ALLERGY								
Research Grants:								
Noncompeting.....	815	44,219	1013	59,544	821	47,031	-192	-12,513
Competing.....	404	24,914						
Contracts:								
Noncompeting.....	106	9,739	119	10,940	106	9,739	-13	-1,201
Competing.....	34	3,149						
Total:								
Noncompeting.....	921	53,958	1132	70,484	927	56,770	-205	-13,714
Competing.....	438	28,063						

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1976 GRANT AND CONTRACT COMMITMENTS - Cont'd
(Dollars in thousands)

	1975 Comparable		1976 Commitments		1976 Budget Request		Difference	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
GENERAL MEDICAL SCIENCES								
Research Grants:								
Noncompeting.....	1164	$86,191	1434	$104,950	1369	$100,931	-65	-$4,019
Competing.....	665	38,668						
Contracts:								
Noncompeting.....	10	3,781	9	3,000	9	3,000	--	---
Competing.....	2	212						
Total:								
Noncompeting.....	1174	89,972	1443	107,950	1378	103,931	-65	-4,019
Competing.....	667	38,880						
CHILD HEALTH								
Research Grants:								
Noncompeting.....	674	49,186	947	68,830	620	49,346	-327	-19,484
Competing.....	497	29,298						
Contracts:								
Noncompeting.....	164	15,327	172	15,975	172	15,975	--	---
Competing.....	40	3,716						
Total:								
Noncompeting.....	838	64,513	1119	84,805	792	65,321	-327	-19,484
Competing.....	537	33,014						
AGING								
Research Grants:								
Noncompeting.....	44	3,973	81	7,757	61	6,183	-20	-1,574
Competing.....	49	3,717						
Contracts:								
Noncompeting.....	8	550	9	630	9	630	--	---
Competing.....	4	250						
Total:								
Noncompeting.....	52	4,523	90	8,387	70	6,813	-20	-1,574
Competing.....	53	3,967						
EYE								
Research Grants:								
Noncompeting.....	318	18,139	435	27,467	347	20,781	-88	-6,686
Competing.....	173	11,420						
Contracts:								
Noncompeting.....	20	2,072	25	2,322	25	2,322	--	---
Competing.....	5	250						
Total:								
Noncompeting.....	338	20,211	460	29,789	372	23,103	-88	-6,686
Competing.....	178	11,670						
ENVIRONMENTAL HEALTH								
Research Grants:								
Noncompeting.....	133	12,832	172	17,987	118	14,227	-54	-3,760
Competing.....	67	4,770						
Contracts:								
Noncompeting.....	15	1,670	19	2,647	17	1,647	-2	-1,000
Competing.....	10	1,279						
Total:								
Noncompeting.....	148	14,502	191	20,634	135	15,874	-56	-4,760
Competing.....	77	6,049						
RESEARCH RESOURCES								
Research Grants:								
Noncompeting.....	654	92,982	693	134,534	232	60,337	-461	-74,197
Competing.....	96	28,290						
Contracts:								
Noncompeting.....	17	2,409	18	3,203	18	2,354	--	-849
Competing.....	5	1,481						
Total:								
Noncompeting.....	671	95,391	711	137,737	250	62,691	-461	-75,046
Competing.....	101	29,771						

1976 GRANT AND CONTRACT COMMITMENTS - Cont'd
(Dollars in thousands)

	1975 Comparable		1976 Commitments		1976 Budget Request		Difference	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
SUBTOTAL, RESEARCH								
Research Grants:								
Noncompeting...	8599	$747,592[1/]	10855	$991,684	8090	$751,784	-2765	-$239,900
Competing.....	4982	394,690						
Contracts:								
Noncompeting...	1544	287,153	1707	320,656	1536	279,400	-171	-41,256
Competing.....	356	61,720						
Total Research:								
Noncompeting...	10143	1,034,745	12562	1,312,340	9626	1,031,184	-2936	-281,156
Competing.....	5338	456,410						
LIBRARY OF MEDICINE								
MLA Grants:								
Noncompeting...	63	4,743	72	5,107	55	4,409	-17	-698
Competing.....	59	1,590						
Contracts:								
Noncompeting...	17	2,025	18	2,200	17	2,025	-1	-175
Competing.....	--	---						
Total:								
Noncompeting...	80	4,743	90	7,307	72	6,434	-18	-873
Competing.....	59	1,590						
CANCER CONTROL								
Grants:								
Noncompeting...	1	720	22	5,551	18	4,500	-4	-1,051
Competing.....	25	3,680						
Contracts:								
Noncompeting...	140	29,019	234	48,703	171	35,650	-63	-13,053
Competing.....	73	15,256						
Total:								
Noncompeting...	141	29,739	256	54,254	189	40,150	-67	-14,104
Competing.....	98	18,936						
TOTAL, NIH								
Research Grants:								
Noncompeting...	8663	753,055	10949	1,002,342	8163	760,693	-2786	-241,649
Competing.....	5066	399,960						
Contracts:								
Noncompeting...	1701	318,197	1959	371,559	1724	317,075	-235	-54,484
Competing.....	429	76,976						
TOTAL:								
Noncompeting...	10364	1,069,227	12908	1,373,901	9887	1,077,768	-3021	-296,133
Competing.....	5495	476,936						

1/ Excludes Fogarty International Center
(Gorgas Memorial Laboratory $500 thousand)

Note: The 1976 commitments shown above do not include, for several Institutes, certain "centers" or "resources" that once initiated are expected to remain open and active. These resources will normally be funded when periodically they revert to "competing" status.

COMPARISON BETWEEN NHLI AND NCI BUDGETS

Mr. FLOOD. Doctor, in the budget justification for the Heart and Lung Institute, there is this statement. Let me read it:

> For more than 50 years heart and blood vessel diseases have been the major causes of death in this country. They now account for 54 percent of all deaths annually. This is three times the deaths from cancer, the next highest.

In the light of that statement, how do you explain the fact that the Heart Institute budget is only 50 percent of the investment in the Cancer Institute?

Dr. LAMONT-HAVERS. I believe, Mr. Chairman, that the relationship between the budgets of the Cancer Institute and the Heart Institute and the other institutes at NIH——

Mr. FLOOD. Let's talk about that. That stands out like a sore thumb.

Dr. LAMONT-HAVERS [continuing]. Is a reflection of the first factor that I mentioned.

The first factor I mentioned as determining the budget of NIH, is the societal pressures and concerns as reflected primarily through the political process. Throughout the history of NIH, we have always noted, even as far back as the early 1930s, that the concern of society have been primarily with cancer and the problems associated with cancer. This led to the establishment, first of all, of the National Cancer Institute. This was later followed by an increasing concern with regard to heart problems and then with other diseases and disabilities.

Therefore I judge, as I look over the history of the past 40 years or so, that our society first fears cancer, and the next fear is heart, and that is where they put their priorities.

Mr. FLOOD. You speak of the question of society, but you also stressed all through your affirmative statement realinement of priorities, the importance of setting priorities.

Dr. LAMONT-HAVERS. I think, as I have indicated, that in setting those priorities one has to keep in mind the concerns of the citizens of this country. One just can't set the priorities with regard to expenditures of tax money without taking these concerns into account.

Mr. FLOOD. Fine, you balance the equities.

Dr. LAMONT-HAVERS. Right.

Mr. FLOOD. To what extent, are you prepared to balance these scales? You put quite a weight and emphasis upon the reactions and concerns of society; is that it?

Dr. LAMONT-HAVERS. Very much so.

Mr. FLOOD. I guess it speaks for itself though, doesn't it?

Dr. LAMONT-HAVERS. I think that the actions both of the Congress and of the Administration are often reactions to such concerns within our society.

NIH HIRING FREEZE

Mr. FLOOD. I understand NIH has been operating under a hiring freeze.

What is the impact of this freeze on your overall operations?

Dr. LAMONT-HAVERS. The impact of the personnel restrictions have now been of concern to the Directors of each of the NIH Institutes for the past number of years. If one looks at the increasing funds and

increasing missions which have been given to NIH since 1968, and compares that to the personnel resources available, one will see that there is a disparity. We have done, I think, as effective a job as possible in the reallocation of those resources, but there is a problem.

Mr. FLOOD. How does your employment ceiling for the current year compare with last year's ceiling?

Dr. LAMONT-HAVERS. Our present ceiling is 10,451 as compared to 10,616.

Mr. FLOOD. Again just for the record, give us a table listing each of the Institute's employment ceilings for 1974, 1975, and 1976.

Dr. LAMONT-HAVERS. Yes, sir.

[The information follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
NATIONAL INSTITUTES OF HEALTH

1976 Budgeted Positions (Comparable)
(Full-time Permanent)

	1974 Actual		1975 Estimate		1976 Estimate	
	Budgeted Positions	Employ. 6/30/74	Budgeted Positions	Employ. Ceiling	Budgeted Positions	Employ. Ceiling
National Cancer Institute	1,832	1,805	1,906	1,818	1,836	1,818
National Heart and Lung Institite	660	689	711	683	691	683
National Institute of Dental Research	267	269	272	262	268	262
National Institute of Arthritis, Metabolism, and Digestive Diseases	555	560	566	556	556	556
National Institute of Neurological and Communicative Disorders and Stroke	518	530	513	515	510	515
National Institute of Allergy and Infectious Diseases	593	595	593	585	587	585
National Institute of General Medical Sciences	155	135	155	148	152	148
National Institute of Child Health and Human Development	338	519	358	512	349	334
National Institute on Aging	179	---	175	---	173	178
National Eye Institute	128	128	142	131	132	131
National Institute of Environmental Health Sciences	236	237	240	240	238	240
Research Resources	72	71	75	69	72	69
John E. Fogarty International Center for Advanced Study in the Health Sciences	49	49	51	48	49	48
National Library of Medicine	467	468	475	458	468	458
Office of the Director	547	520	549	528	546	528
NIH Management Fund	3,277	3,398	3,301	3,285	3,316	3,285
Survice and Supply Fund	628	643	626	613	614	613
Total, National Institutes of Health	10,501	10,616	10,708	10,451	10,557	10,451

Mr. FLOOD. Now, the Biomedical and Behavioral Research Training Act—that is, Public Law 93-348—requires HEW to conduct a study to establish: (A) The Nation's overall need for biomedical and behavioral research personnel; (B) the subject areas in which such personnel are needed, and the number of such personnel needed in these areas; and (C) the kinds and the extent of training which shall be provided such personnel.

Doctor, that report was due on March 31.

Can you summarize for us now the contents of that report?

Dr. LAMONT-HAVERS. The legislation also required that the National Academy of Sciences be asked to undertake this study, and we have arranged for them to do so. Such a study is a very difficult thing to do. The Academy therefore wanted to conduct a feasibility study to find out whether indeed they could do it. This was finished, and we received the result of the feasibility study by the Academy in late February or early March. They have agreed to undertake the manpower study, and they are doing so right now.

Mr. FLOOD. Can you hit the highlights?

Dr. LAMONT-HAVERS. Yes.

Mr. FLOOD. Can you summarize it?

Dr. LAMONT-HAVERS. What they feel is that it is feasible to determine those areas within biomedical research in which manpower is short and which should have a high priority. That will be the first determination, so that by July 1 we will have a preliminary report from them, outlining those areas, and we can then start operating within fiscal year 1976.

Mr. FLOOD. That was due March 31?

Dr. LAMONT-HAVERS. Yes; but that was an impossible date to meet. I think it is March 31 of each year.

Mr. FLOOD. Will you supply a copy of that report for the record?

Dr. LAMONT-HAVERS. I certainly will; yes, sir.

[The information follows:]

Insert page 3089A

R E P O R T

of the

COMMITTEE ON A FEASIBILITY STUDY OF NATIONAL NEEDS FOR BIOMEDICAL AND BEHAVIORAL RESEARCH PERSONNEL

* * *

COMMISSION ON HUMAN RESOURCES

NATIONAL RESEARCH COUNCIL

February 1, 1975

PREFACE

The National Research Service Award Act of 1974 articulates the view of Congress that direct support of training for careers in biomedical and behavioral research is an appropriate and necessary role for the Federal Government. It signals at the same time the importance of careful planning for an era in which the growth of research training programs is likely to be more limited. In this connection, a novel element in the legislation is the stipulation that training awards by the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration are to be restricted, after July 1, 1975, to subject areas for which there is a need for personnel. The vehicle for determining personnel needs is to be a continuing study, the objectives of which are prescribed in the law.

The present report, prepared in response to a request from the Secretary of Health, Education, and Welfare, describes the rationale for the Committee's conclusion that such a study is feasible of accomplishment. In proposing a course of action for consideration by the Governing Board of the National Research Council, the report identifies the initial steps that can be reasonably undertaken within the limitations of the current data base and available methodology. In addition, it outlines an organizational framework and formulates a first-year budget tied to explicit assumptions as to distribution of responsibility between the National Research Council and the two operating agencies.

Although the report highlights a number of questions concerning the difficulty of projecting needs, the Committee acknowledges that some must be left to be discussed by the continuing study. The report, however, expresses the Committee's belief that training programs in the biomedical and behavioral sciences can be usefully guided by such study of future requirements. Consistent with that belief, the Committee recommends an early start toward developing the informational and judgmental basis that must undergird a continuing study.

In carrying out the feasibility study, the Committee received help from many quarters. Members of the eight advisory panels, despite severe time constraints, were able to shed considerable light on problems of methodology and issues unique to the various categories of biomedical and behavioral sciences. Many individuals and professional associations were helpful in making suggestions and in sharing the lessons derived from their own experiences in the performance of manpower studies. The National Institutes of Health provided support for the study, and the assistance of members of the NIH/ADAMHA staffs in providing data is gratefully acknowledged. The Committee's deliberations were greatly enriched through the guidance and advice provided throughout the project by Dr. Robert A. Alberty and Dr. William C. Kelly. Finally, it is a pleasure to acknowledge the contributions of Dr. Samuel Herman, who served as staff director for the project, as well as those of Mr. Robert G. Lindee in his capacity of consultant for the study.

Robert J. Glaser, M.D.

February 1, 1975

THE COMMITTEE

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I. INTRODUCTION

This report concerns the feasibility of estimating national needs for research personnel in the biomedical and behavioral sciences. The President on July 12, 1974, signed the National Research Act (P. L. 93-348). Title I of which* amends the Public Health Service Act "to establish a program of National Research Service Awards to assure the continued excellence of biomedical and behavioral research".

The new legislation authorizes awards for predoctoral and postdoctoral research training both to individuals and to non-Federal public or nonprofit institutions (which will select individuals for such awards). Not less than 25 percent of the amount appropriated must be made available directly to individuals. Award recipients must give assurance that they will meet a service requirement---engage in health research or teaching or, alternatively, (1) serve as a member of the National Health Service Corps, (2) serve in his or her specialty in a geographic shortage area in that specialty or in a health maintenance organization which offers care in a medically underserved area, or (3) serve in an approved health-related activity. Guidelines now in preparation will specify the period of time within which repayment may be made, the type of research and teaching which qualify as payback, and other matters relating to service payback. Recipients who fail to comply with the service requirement must repay the amount of their awards plus interest, less proportionate credit for half of the months they actually served.

Effective July 1, 1975, awards under Title I may be made for research training only in those subject areas in which there is need for personnel, as determined by a continuing study which the Secretary of Health, Education, and Welfare is to request the National Academy of Sciences to conduct. As described in the legislation, the continuing study is "to establish (A) the Nation's overall need for biomedical and behavioral research personnel, (B) the subject areas in which such personnel are needed and the number of such personnel needed in each such area, and (C) the kinds and extent of training which should be provided such personnel". Also to be derived from the continuing study is an assessment of current training programs, as well as identification of the kinds of research positions available to and held by recipients of National Research Service awards. An annual report of the continuing study is to be submitted by the Secretary to the House Committee on Interstate and Foreign Commerce and the Senate Committee on Labor and Public Welfare not later than March 31 of each year.

In response to a request from the Secretary, the Governing Board of the National Research Council (NRC) voted on September 16, 1974, to authorize the Commission on Human Resources to explore the feasibility of a continuing study. The feasibility study was initiated shortly thereafter with contract support from the National Institutes of Health (NIH), to which agency lead responsibility had been assigned by the Secretary for developing a plan to implement the provisions of Title I of the Act.

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*Title I, cited as the National Research Service Award Act of 1974, repeals existing research training and fellowship authorities of the National Institutes of Health (NIH) and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). Henceforth, research training activities of these agencies will be carried out under a consolidated authority contained in the new law. Title I does not address clinical training, nor does it affect authority available elsewhere in the Public Health Service Act under which the Secretary may enter into contracts with public and private entities and individuals for health services research and health statistics training.

Following discussions with representatives of the Assembly of Behavioral and Social Sciences, the Assembly of Life Sciences, and the Institute of Medicine, a Committee on a Feasibility Study of National Needs for Biomedical and Behavioral Research Personnel (Appendix A) was appointed to supervise conduct of the feasibility study. To advise the Committee, panels were established for the following five disciplinary areas into which were grouped the various fields of research training support by NIH and ADAMHA: Basic Medical Sciences, Basic and Applied Biology, Behavioral Sciences, Clinical Sciences, and Health Services Research and Evaluation (Appendix B). In addition, three panels concerned with methodology were set up under the following titles: Data and Analyses, Supporting Studies, and Impacts of Training (Appendix B). Administrative support for committee and panel functions has been provided by staff of the Commission with the assistance of a consultant who was available on essentially a full-time basis. To prepare the ground for committee operations, discussions were held with staff of the cognizant Congressional Committees, professional and education associations, Sections of the National Academy of Sciences, and NIH/ADAMHA representatives. Liaison officers designated by NIH/ADAMHA provided a substantial body of program data, as well as interpretation of policies and procedures of the two agencies.

Completion of the report was targeted for December 31, 1974. In light of the complexity of the overall task, however, the request for support of the feasibility project anticipated a possible need for extension of time to February 28, 1975, with the feasibility report itself to be completed in early February. Consideration of the report by the Governing Board of the National Research Council would then lead to a decision concerning acceptance of the request to conduct a continuing study.

II. EARLIER EFFORTS TO ESTIMATE NATIONAL NEEDS

Various Federal agencies have attempted to forecast the goodness of fit between supply and demand, to project supply and/or demand, and to estimate the personnel requirements for subject fields in broad and fine detail. The Bureau of Labor Statistics has projected requirements from 1968 to 1980 for doctoral scientists and engineers in private industry, based on a questionnaire study of major employers (1). It also has made projections of long-term trends in industrial and occupational growth based on a seven-step projection model which incorporates factors affecting the whole economy.

The National Science Foundation has completed two studies---and has a third in preparation---on the projected relationship between supply and utilization of science and engineering doctorates, based upon supply trends for six preceding years and explicit assumptions concerning rates of increase in the Gross National Product, funds to be expended on research and development, and employment requirements for academic and nonacademic positions (2).

In terms of direct relevance to the present area of inquiry, several publications of the National Institutes of Health merit special attention. Two reports, issued in 1963 and 1968 respectively, used an "updated" benchmark approach (3, 4). A base-year employment benchmark was established separately for government, industry, and non-profit institutions, classified by level of training. Annual projections of undergraduate and graduate enrollment and of M.D. candidate enrollment were used to extend the benchmark figures, with stated assumptions as to degree completion rates, educational progression rates, and age-cohort survival rates.

In January, 1970, the National Institutes of Health published projections for the period 1972-1980 to show trainee populations required to sustain several assumed alternate growth rates of research funding, with provision for deaths, retirements, and shifts to other activities (5). The essential contribution of this model was its use of separate estimates for research, teaching, service, administration, and other functions. A more sophisticated version of this model, including estimates of prospective demand for biomedical scientists through FY 1983, was released in 1972 (6).

Numerous studies in the private sector have also been addressed to these problems. Cartter has made the most detailed analysis of expected faculty needs for holders of the Ph.D. He has projected, by five-year intervals, the number of doctor's degrees to be awarded, the number of new faculty members who should hold that degree to match the increasing enrollment and to maintain the current percentage of doctorate holders in the Nation's faculty, and the percentage of new doctorates of each five-year period who would be required for such faculty appointments (7). Freeman has made projections for various fields with a market model that takes into account the behavioral characteristics of performers in the labor market (8). The status of such labor market forecasts for doctorates is discussed in a report of the National Board on Graduate Education (9). In addition, Freeman and Breneman have examined current forecasting techniques against a background of past forecasting failures, and have described a methodology for making "response adjusted" projections, based on student career decisions, experienced personnel supply behavior, employer decisions, and salary determinations (10). The National Planning Association has undertaken a pilot study to assess the potential for anticipating the scientific manpower requirements likely to be generated by expenditures in pursuit of national goals in the private economy in the next five-ten years. A special NPA case study concerns requirements in the 1980's for scientists and engineers for the abatement of air, water, and solid waste pollution (11). Also of interest in this connection is a demand survey for industry which was sponsored in 1972 by the Industrial Research Institute (12).

A careful review of these diverse efforts leads to several observations and conclusions:

1. Projections must be distinguished from predictions. Derived from models based on trends and awareness of current developments, projections offer a range of possible future events based on explicit assumptions and no significant break in trends. It is important that no false sense of precision be attributed to projected numbers in view of the limitation of the data and methodologies, the complexity of manpower utilization, and the unpredictability of future events.

2. Projections of forecasts of supply and demand for highly trained manpower have focused on numbers and given relatively little attention to quality ---quality of instruction, research, or of the Ph.D.'s themselves. Assaying quality is a difficult problem. There are at present only rough methods for taking this attribute into account, such as assuming that the quality of institutions or departments can be measured, and that on the whole institutional quality is related to the quality of those who are awarded degrees.

3. The results of attempts to produce supply and demand forecasts by field and discipline have been spotty. Sizable differences between projected estimates and actuality are not uncommon. Although relatively sophisticated analyses have been made by some professional associations---in physics, in surgery, and in pharmacology and experimental therapeutics, for example---many lack the resources to undertake these activities. Further studies of forecasting for specific fields are clearly needed to throw light on the conceptual, methodological, and practical problems of forecasting by discipline.

4. One of the central problems of projections is the difficulty of formulating generally acceptable concepts of underemployment. Specifically, there is a need to determine the criteria by which underemployment is to be defined, and to attach quantities to the criteria to permit enumeration of the underemployed. A number of criteria could be used, such as differential income and extent of utilization of maximum skills.

5. In addition to methodologic complexity and data shortcomings that plague the projector, there is the well-known fact that published projections are viewed as predictions by the public and the market moves to defeat the predictions. Employers and prospective employees note where "shortages" or "overages" are forecast and shape their strategies accordingly.

6. A significant development in projecting the supply of, and demand for, high-level manpower has been the increasing attention paid to market forces and the behavior of individuals and institutions in the market. Extension of this work has a high potential for the improvement and refinement of projections.

III. PRINCIPLES

A number of general principles have emerged from the Committee's discussions and have been found helpful in guiding its recommendations.

A. Numbers

Assessment of the Nation's needs for biomedical and behavioral research personnel is a necessary task in view of the large national interest in this area and the need to use national resources wisely. It is also a difficult task that must be approached with a clear recognition of the difficulties. The Committee and its panels believe, however, that the present methodology and data base are adequate for developing a strategy and for making a start toward forecasting aggregate manpower requirements for biomedical/behavioral research. Even though use of particular assumptions may introduce an appreciable margin of error at the outset, available methodology and the data base are adequate to indicate the direction of change.

In contrast to the problem of forecasting aggregate manpower in large fields, estimating needs by fine fields is exceedingly difficult. Boundaries between disciplines have become less distinct with the increase in emphasis

on study of biological phenomena at the molecular level. Titles of narrow disciplinary fields have therefore lost some meaning for the purposes of forecasting. The problem is compounded by the difficulty of predicting major scientific developments and their impact on manpower requirements. Moreover, many aspects of the dynamics of the manpower pool are not clearly understood, and hence any supply/demand/model that can be developed will have limitations for determining the need for disciplinary specialists. These limitations, the Committee believes, are offset largely by the breadth of training and the adaptability of biomedical/behavioral scientists and their capacity for mobility within and across fields. This is especially true for transfers from more fundamental to applied fields. Further, postdoctoral training often makes possible a transfer to a related field where shortages may exist. As noted in The Life Sciences, a report published by the National Academy of Sciences, a large percentage of those pursuing postdoctoral training seek this experience in a discipline other than that in which they received their graduate education (13). Moreover, most do so in laboratories other than those of their original research mentors, engaging in fields of research distinctly different from those in which they had been trained in the first instance. These facts underscore the importance of postdoctoral study as a mechanism for responding to new opportunities.

B. High Quality and Stability

In addition to a concern with adequate numbers of personnel, NIH/ADAMHA has a pivotal role in helping to maintain high-quality training programs. This dual role, the importance of which is underscored in the declaration of purpose for Title I of the law, requires continuity of support for its proper fulfillment. Since it takes many years to complete the training of an individual---five or more years of post-baccalaureate training for Ph.D.'s working in the basic biomedical and behavioral sciences---the process cannot be turned on and off abruptly without damage to quality and training capability. Persistence of the stop/start pattern of support that has occurred in recent years could lead to erosion in the quality of the training structure. In this regard, the Committee believes the continuing study should include an historical survey of factors that have contributed to instability and should document the effects of instability on faculty and the scientific environment, physical facilities, and the recruitment and retention of promising trainees. It may be possible, independent of the level of support, to design experimental situations to test the effectiveness of alternative funding arrangements in promoting stability.

C. Flexibility

It will continue to be important to foster flexibility in the organization of training activities to ensure responsiveness to the changing character of the research scene. Change must not only be permitted but encouraged to allow appropriate response to the dynamic character of biomedical/behavioral research and its changing manpower requirements. Within funding levels tied to specific fields and numbers, how are resources to be mobilized to allow ready responsiveness to emerging opportunities? This is a key question requiring the development of a sensitive monitoring system, as well as the introduction of modifications and the design of experimental training programs. Study approaches could include a comparison of disciplinary versus interdisciplinary programs as a means of responding to changing manpower needs.

Flexibility in this context has implications which the Committee believes will merit consideration in a continuing study. A key issue relates to the capability of institutions to adjust their resources---faculty, students, and facilities---to a changing manpower outlook, as in the case of fields approaching a point of saturation.

D. Concern for Excellence

The new law assigns to the continuing study the task of assessing NIH/ADAMHA training programs---a further indication of the concern for excellence. The study will be expected to evaluate the impact of training programs on the total scientific environment of institutions. Basic approaches to implementing this responsibility will be to identify areas of program success for retrospective examination of effects, such as encouragement of programs that cut across traditional departmental lines; stimulation of interaction of faculty, trainees, and persons from other departments and institutions; and increase in the quality of advanced courses. Other questions warrant investigation. Is quality more effectively fostered by concentration on a limited number of programs than by providing broad support for training? Is it possible without NIH/ADAMHA support to build the types of curricula that permit quality training in special fields? How effective have these programs been in attracting superior personnel into areas lacking a tradition of research?

E. Shared Responsibility

Though it should be a truism, the point merits repetition that NIH/ADAMHA are not---and should not be---responsible for the support of all biomedical and behavioral research training. That responsibility is shared with other elements of American society---the states, industry, the foundations, private donors, and the universities themselves---which will continue to rule their individual contributions. NIH/ADAMHA are indeed responsible, as affirmed by the new law, for providing sufficient support to ensure that the overall training effort will produce the numbers and quality of research scientists which forecasts suggest will be required in the future. This presupposes that NIH/ADAMHA will continue to bear a substantial share of the costs of graduate education in the biomedical/behavioral sciences with provision for adjustment in the face of evidence of excessive or insufficient training effort.

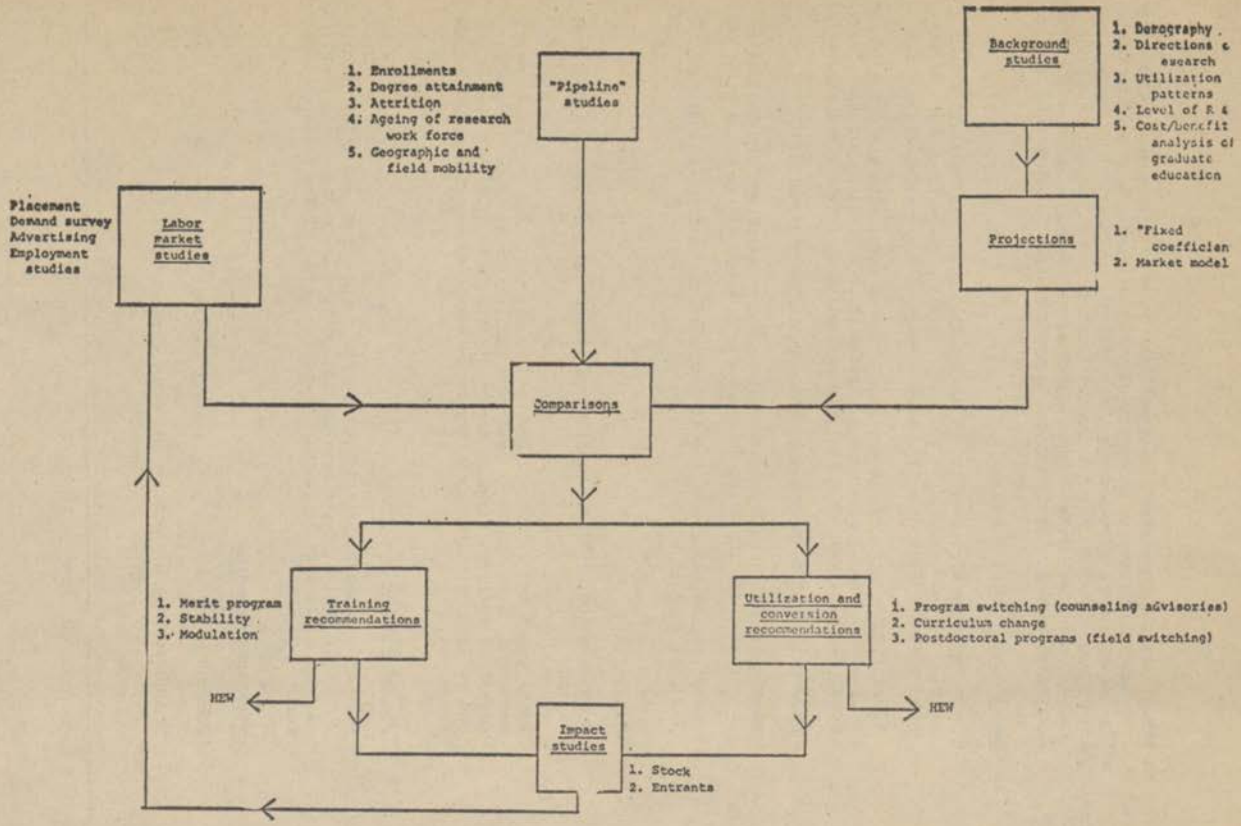
IV. A CONCEPTUAL FRAMEWORK

The Committee focused its attention on an eclectic, pluralistic approach designed to bring together information and seasoned judgment from a number of different sources to permit testing of tentative findings of national need and eventual formulation of recommendations. Although there are promising developments in forecasting personnel needs, particularly in the use of models that take market forces and individual and institutional behavior into account, the Committee is not convinced that the outputs of such comprehensive models are as yet sufficiently reliable to fulfill requirements of the law.

To illustrate the Committee's approach, the relationships among a number of possible sources of information and types of analyses are shown in a block diagram (Figure 1). Although the arrows suggest a cybernetic approach, the diagram is in reality less precise than this since many of the units have multiple connections that are not depicted and since the units themselves are quite complex. The types off activity represented by the individual blocks may be outlined as follows:*

- Background Studies
  - Demographic analysis of trends in university and professional school enrollment rates and on anticipated sizes of groups from which enrollment will be drawn---to establish the need for new faculty.
  - Identification of new and emerging research areas with potential impact on manpower requirements---e.g., research on biological effects of environmental chemicals as a basis for establishing criteria and standards.
  - Examination of manpower utilization patterns in research.
  - Examination of trends in expenditures for research and development---the single most important determinant of demand for research personnel.
  - Cost/benefit analyses to try to determine the returns on investment in graduate education.
- Projections
  - Consideration of "fixed coefficient" models of the education/manpower system.
  - Development and testing of "market" models that take into account student choices of fields of study and initial job decisions; decisions of persons already in the work force; employer hiring, firing, promotion and retirement policies; salary data; and governmental initiatives and responses.
- Pipeline Studies
  - Flow of personnel through graduate and postdoctoral education into employment, including analyses of enrollment data, degree attainment, attrition, field switching, and turnover and aging of the research work force.
- Labor-Market Studies
  - Monitoring of various job placement services.
  - Demand surveys of industry and other employment sectors.

*Labels correspond to those in Figure 1.


Background studies
1. Demography
2. Directions of research
3. Utilization patterns
4. Level of R & D
5. Cost/benefit analysis of graduate education
"Pipeline" studies
1. Enrollments
2. Degree attainment
3. Attrition
4. Ageing of research work force
5. Geographic and field mobility
Projections
1. "Fixed coefficien
2. Market model
Placement
Demand survey
Advertising
Employment studies
Labor market studies
Comparisons
1. Merit program
2. Stability
3. Modulation
Training recommendations
Utilization and conversion recommendations
1. Program switching (counseling advisories)
2. Curriculum change
3. Postdoctoral programs (field switching)
HEW
HEW
Impact studies
1. Stock
2. Entrants

- Monitoring of fluctuations in the Engineer/Scientist Demand Index (ESDI) reflecting the volume of recruitment advertising in technical journals and newspapers.

- Assimilation of the results of employment studies such as the National Research Council's Survey of Doctoral Scientists and Engineers and the surveys made by professional societies.

• Impact Studies

- Studies of the impacts of these and other support programs on the market undertaken in collaboration with education and professional associations and other agencies. Also, studies directed toward identifying the effects of NIH/ADAMHA training programs on faculty, curriculum, physical facilities, development of interdisciplinary programs, baccalaureate-to-doctorate time lapse, Ph.D. attainment rate, and post-training career outcomes.

• Comparisons

- This block encompasses the principal function to be performed by the committee for the continuing study and the committee's panels. Within the framework shown, the Committee would be expected to draft annually a "State of National Need" document which would be based on the results of the study outlined above. The end product would take the form of a description of field requirements that had been subjected to as many realistic tests as possible and that represented the best effort of the Committee in estimating needs for at least the near-term future.

• Recommendations

The comparison process would generate recommendations of two kinds:

- Training Recommendations would have to do with predoctoral and postdoctoral traineeships and fellowships to be awarded by the Federal government. Three principles might well be observed: (1) recognition of unusual merit or promise of individuals through a small, highly selective, nationally competitive fellowship program; (2) stability of support through an appreciably larger training grant program in which institutional needs would be recognized and field support changed relatively slowly; and (3) modulation of field support levels---e.g., fluctuations of an appropriate percentage consistent with the committee's perceptions as to where shortages or overages of personnel were occurring or likely to occur.

- Since the time needed for effecting change in output through the predoctoral support mechanism is approximately five years, a need exists for a mechanism that can respond to national needs more quickly---in one or two years. Utilization and Conversion Recommendations might therefore be made through the medium of (1) program advisories to encourage field switching at the postdoctoral and, to the extent possible, at the

advanced predoctoral levels; (2) suggestions for curriculum change to meet new needs; and (3) most importantly, the award of postdoctoral fellowships and traineeships to facilitate field switching and to smooth out market fluctuations.

The two types of recommendations would be transmitted in annual reports to the Secretary (and to the academic community).

V. OBJECTIVES

The major foci of a continuing study of national needs will be aggregate numbers, estimates by fields---and, where possible, subfields---stability, flexibility, and excellence. While closely interrelated, study approaches along these dimensions will vary, as will the time frame for their accomplishment. In view of the time constraints set by law, it is therefore necessary to distinguish between activities to be undertaken in an initial period extending from March 1, 1975, to June 30, 1975, and those to be addressed over the longer term.

A. Initial Objectives

The immediate need is for aggregate projections for the biomedical/behavioral sciences and for estimates by major field, leading to recommendations of levels of training support.

Aggregate projections. The Committee believes it feasible to project demand for biomedical and behavioral research personnel, based on suitable assumptions concerning levels of research support, by allowing the analysis to be directed by demographic factors and by expert judgments concerning the emergence of new areas of knowledge and technology. In addition, it seems feasible in the initial period to develop econometric models of supply and demand in these fields, using national time-series data for the biomedical and behavioral sciences in the aggregate, and to test such models for their applicability. In particular, one of these models would involve the use of relative-salary data. Models of this type have been used with some degree of success to provide estimates for physics, engineering, and law. Following the strategy of previous scientific manpower model-building developed by Freeman and others, the Committee would seek to use available data on degrees, salaries, R&D expenditures, enrollment, etc., to forecast supply and demand contingent upon exogeneous policy variables.

It will be essential in making these projections to take into account changing opportunities and demand for women and members of minority groups within the Nation's biomedical/behavioral research programs.

Field projections. Since adequate studies exist on the numbers of doctoral degrees awarded by field each year, short-term projections can be attempted during the initial period of continuing study. The feasibility of making forecasts by field, as suggested under III-A above, has limitations. The narrower the fields covered, the greater will be the problem of substitutability. Another way of stating the problem is that the number of those with direct training in a given field is an inadequate measure of the supply

of persons capable of working in that field. Moreover, the further into the future that forecasts are made, the greater the barriers to measuring supply in narrowly defined fields.

The margin of error may be minimized through projecting by broad fields in contrast to aggregating subfields. Broad-field projections can be supplemented by judgments of expert panels to delineate rapidly growing fields and those showing a more modest or relatively slow growth or decline. Although not currently available, models analogous to those referred to above can be developed relatively early for selected fields and subfields and to a limited degree could be made to reflect the extent to which workers could shift among fields. This analysis would make use of field-switching data developed by the National Research Council and other organizations.

Levels of training support. Based on the foregoing projections and examination of current trends in supply---including the output of other training efforts---recommendations would be made for the levels of NIH/ADAMHA training programs in FY 1976. As in the case of the projections of demand, these would be made by broad field.

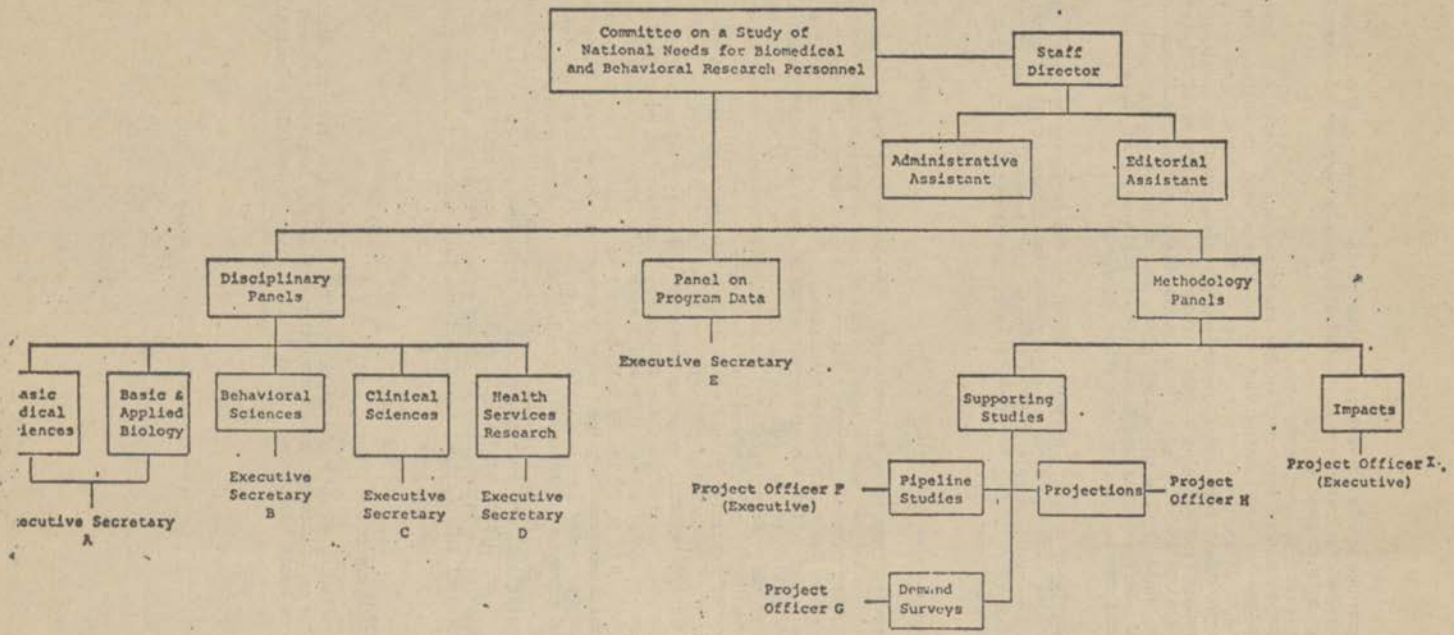
B. Longer-term Objectives

Special importance is attached to improvement of the data base and continued refinement of methodology. Over the next several years, the full potential of the plan diagrammed in Figure 1 seems likely to be realized and should provide the basis needed for increasingly detailed recommendations by the Committee. The usefulness of current studies, such as the NRC-maintained Roster of Doctoral Scientists and Engineers, could be significantly enhanced for purposes of the continuing study. A suitable enlargement of the survey sample size would help to ensure representativeness of employment data for a greater variety of subfields in the biomedical/behavioral sciences. With respect to methodology, a detailed analysis can be made of the specific features of the biomedical/behavioral manpower market and second-round model-building can be designed to incorporate these features. Studies of manpower flow in academic medicine need to be made. It would also be desirable to conduct a study comparing the number of the Ph.D.'s awarded as a percentage of the number of baccalaureate degrees in prior years to determine the effect of support programs. Other steps would involve bringing to bear on supply/demand problems the expertise of persons in the market (academic deans, department chairmen, students, and research directors). The continuing study would involve also a more careful analysis of the characteristics of different sectors of the market and modes of adjustment to changing market and support conditions than has been possible in the past. The use of non-salary adjustment mechanisms, such as postdoctoral fellowships, could be taken into account in the economic modeling.

VI. PROJECT ORGANIZATION

The continuing study would be carried out within the framework outlined in Figure 1 under a committee and panel structure within the National Research Council's Commission on Human Resources. Figure 2 illustrates a possible organizational plan.

FIGURE 2. AN ORGANIZATIONAL STRUCTURE



The NRC would carry the sole responsibility for analysis of program data, supporting studies of several kinds, impact studies, "needs statements", comparisons with a variety of test data, and recommendations. Under certain circumstances outside organizations may be engaged to perform selected tasks. The results would be communicated to the Secretary in a series of annual reports, to be transmitted to the Congress.

The Committee believes that the activities for which NRC has sole and shared responsibility could be carried out with an annual budget initially of about $1 million (Table 1). The anticipated number of professional staff members required would be 12, and a supporting staff of 15 members would also be needed. The Committee would meet monthly at the start, and the panels at quarterly intervals.

TABLE 1. Estimate of Initial Annual Costs

Personal Services	$435,000
Fringe Benefits	56,600
Consultants	12,500
Committee & Panel Travel	66,000
Consultant Travel	4,000
Staff Travel	10,000
Communications & Shipping	7,200
Materials & Services	7,200
Commissioned Studies	100,000
Data Processing	36,000
Indirect Costs	264,400
Total	$998,900

Maintenance of administrative records of training awards would be the responsibility of NIH/ADAMHA. Extramural performers operating under NIH/ADAMHA or organizations conducting commissioned studies for the NRC would address other needs for data and analysis.

VII. RECOMMENDATIONS

A. The Committee recommends that the National Academy of Sciences accept the invitation of the Secretary to conduct the continuing study mandated by Title I of the National Research Act. The recommendation is based on the belief: (1) that within the methodologic limitations outlined in this report a productive start can be made during the current fiscal year toward meeting the requirements specified in the law; (2) that improvements can be expected in ability to gather and utilize needed information as experience is gained over the next several years; and (3) that the National Research Council through the experience of its Commission on Human Resources and its ability to call upon the skills of the scientific community is the most appropriate agency to conduct the continuing study. The recommendation further assumes that sufficient agreement can be reached on the conditions for the study as outlined below.

B. The continuing study is viewed as a long-term undertaking with major costs that may involve at least three-year obligations. It is the Committee's view, particularly in light of the single-year authorization contained in the Act, that discussions be conducted with Congressional and Departmental staff regarding a three-year commitment for continued support of the study.

C. An appropriate level of effort for an undertaking of the magnitude envisioned in this report calls not only for the continuing study by the National Research Council but also for data collection by NIH/ADAMHA and extramural research by other organizations. The Committee believes that an amount up to one percent of the ceiling authorized by law can be justified to support such a level of effort, including a need in the initial year for approximately $1 million to underwrite the National Research Council's continuing study.

D. The current legislation contains several provisions with which NIH/ADAMHA has had little or no experience in the administration of training programs. The Committee recommends that the effect of these provisions on the program, notably the need for annual renewal of authorization, payback requirements, and the specification of 25 percent of the appropriation for direct award to individuals, be examined carefully by the committee for the continuing study. An additional point that will merit scrutiny is the 3-year limitation on support of any individual, particularly its impact on activities such as the Medical Scientist Training Program and most predoctoral graduate study programs.

E. The present report calls attention to limitations in the adequacy of methods for projection of need for biomedical and behavioral research personnel and for determination of suitable levels of training support. The Committee believes that some of these limitations can be significantly remedied through further studies and that others can be offset by appropriate administrative measures affecting training programs, measures that are responsive to market forces and conditions.

F. Since future requirements for personnel cannot always be predicted, the Committee recommends experimentation with programs at both the predoctoral and postdoctoral levels that can encourage the post-training movement of biomedical/behavioral scientists into specific research areas as opportunities arise, with due regard for individual desires and aspirations.

G. The Committee has noted the National Research Council's current studies of the Nation's population of biomedical and behavioral research personnel and its studies of the number and type of graduate students planning careers as biomedical and behavioral scientists. It suggests the additional need to observe trends at the earlier stages of education as a means of detecting significant fluctuations in the supply of scientific manpower early enough to determine the reasons and permit appropriate policy decisions.

REFERENCES

1. United States Department of Labor. Ph.D. Scientists and Engineers in Private Industry, 1970. Washington, D.C., 1970.

2. National Science Foundation. Science and Engineering Doctorate Supply and Utilization, 1969 and 1980. Washington, D.C., 1971.

3. United States Department of Health, Education, and Welfare. "Resources for Medical Research", Manpower for Medical Research Requirements and Resources. Report No. 3, Washington, D.C., January, 1963.

4. United States Department of Health, Education, and Welfare. "Resources for Medical Research", Biomedical Research Manpower for the Eighties. Report No. 11, Washington, D.C., December, 1968.

5. Issue Paper on the Training Programs of the Institutes of the National Institutes of Health: Part 1, October, 1970.

6. The Training Programs of the Institutes of the National Institutes of Health, Fiscal Year 1974, Volume I, October, 1972.

7. Cartter, A. M. "Scientific Manpower for 1970-1985", Science. 172:132. 1971.

8. Freeman, R. B. The Market for College Trained Manpower. Harvard University Press, Cambridge, Massachusetts, 1971.

9. Doctorate Manpower Forecasts and Policy. A Report of the National Board on Graduate Education, National Academy of Sciences, Washington, D.C., 1973.

10. Forecasting the Ph.D. Labor Market: Pitfalls for Policy, by Richard Freeman and David Breneman. Technical Report No. 2 of the National Board on Graduate Education, National Academy of Sciences, Washington, D.C., 1974.

11. The Demand for Scientific and Technical Manpower in Selected Energy-Related Industries, 1970-1985. National Planning Association, Washington, D.C., 1974.

12. Utilization of and Demand for Engineers and Scientists in Industrial Research. Report of a survey conducted by the Industrial Research Institute, Engineering Manpower Commission of Engineers Joint Council, and Scientific Manpower Commission, 1972. Industrial Research Institute, Inc., New York, New York, 1973.

13. The Life Sciences. Report of Committee on Research in the Life Sciences of the Committee on Science and Public Policy. National Academy of Sciences, Washington, D.C., 1970.

APPENDIX "A"

COMMITTEE ON A FEASIBILITY STUDY OF NATIONAL NEEDS
FOR BIOMEDICAL AND BEHAVIORAL RESEARCH PERSONNEL

Chairman: Robert J. GLASER, M.D.
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Henry J. Kaiser Family Foundation

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irector, Laboratory of Research
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lius H. COMROE, Jr., M.D.
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ward E. DAVID, Jr., Ph.D.
xecutive Vice President
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uld, Inc.

ren DAVIS, Ph.D.
siting Lecturer in Economics
rvard University
rom Brookings Institution)

ul A. MARKS, M.D.
ce President for Health Sciences
rector, Cancer Research Center
lumbia University

vid MECHANIC, Ph.D.
hn Bascom Professor of Sociology
iversity of Wisconsin, Madison

Robert S. MORISON, M.D.
Richard J. Schwartz Professor
of Science and Society
Program on Science, Technology,
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Charles R. Drew Postgraduate
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P. Roy VAGELOS, M.D.
Professor and Chairman
Department of Biological Chemistry
Director, Division of Biology
and Biomedical Sciences
Washington University

APPENDIX "B"

COMMITTEE ON A FEASIBILITY STUDY OF NATIONAL NEEDS
FOR BIOMEDICAL AND BEHAVIORAL RESEARCH PERSONNEL

P A N E L S

BASIC AND APPLIED BIOLOGY

Chairman: H. N. MUNRO, D.Sc.
Massachusetts Institute
of Technology

Lawrence BOGORAD, Ph.D.
Harvard University

Robert H. BUFRIS, Ph.D.
University of Wisconsin

BASIC MEDICAL SCIENCES

Chairman: Robert J. BERLINER, M.D.
Yale University

Vincent P. DOLE, M.D.
Rockefeller University

Donald W. KING, M.D.
Columbia University

Daniel E. KOSHLAND, Jr., Ph.D.
University of California, Berkeley

Salvador E. LURIA, M.D.
Massachusetts Institute of Technology

C. R. PARK, M.D.
Vanderbilt University

Dominick P. PURPURA, M.D.
Albert Einstein College
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Norman WEINER, M.D.
University of Colorado

BEHAVIORAL SCIENCES

Chairman: Gabriel W. LASKER, Ph.D.
Wayne State University

William BEVAN, Ph.D.
Duke University

Edgar F. BORGATTA, Ph.D.
Queens College
City University of New York

Donald R. GRIFFIN, Ph.D.

Howard F. HUNT, Ph.D.
New York State Hospital

Eliot STELLAR, Ph.D.
University of Pennsylvania

CLINICAL SCIENCES

Chairman: David M. KIPNIS, M.D.
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The Johns Hopkins University

Kurt H. ISSELBACHER, M.D.
Harvard University

John F. MURRAY, M.D.
San Francisco General Hospital

Lawrence [illegible]

Helen M. RANNEY, M.D.
University of California
Medical School, San Diego

Rosalyn S. YALOW, M.D.
Veterans Administration
Hospital, Bronx

George D. ZUIDEMA, M.D.
The Johns Hopkins University

DATA AND ANALYSES

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University of Rochester

Wilfrid J. DIXON, Ph.D.
University of California,
Los Angeles

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Harvard University

Robert W. HODGE, Ph.D.
State University of New York,
Stony Brook

Robert McGINNIS, Ph.D.
Cornell University

David L. WALLACE, Ph.D.
University of Chicago

HEALTH SERVICES RESEARCH AND EVALUATION

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Harvard University

John H. BRYANT, M.D.
Columbia University

Robert J. HAGGERTY, Ph.D.
Center for Advanced Study
of the Behavioral Sciences,
Stanford
(on sabbatical from the
University of Rochester)

IMPACTS OF TRAINING

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Hoffmann-La Roche, Inc.

Robert M. BOCK, Ph.D.
University of Wisconsin

Eugene L. HESS, Ph.D.
Federation of American Societies for Experimental Biology

Charles V. KIDD, Ph.D.
Association of American Universities

John F. SHERMAN, Ph.D.
Association of American Medical Colleges

SUPPORTING STUDIES

Chairman: Gordon HAMMES, Ph.D.
Cornell University

James A. DAVIS, Ph.D.
National Opinion Research Center, Chicago

John K. FOLGER, Ph.D.
Tennessee Higher Education Committee

Nancy M. GORDON, Ph.D.
United States Department of Labor

Herbert E. KLARMAN, Ph.D.
New York University

Walter Y. OI, Ph.D.
University of Rochester

Karl F. SCHUESSLER, Ph.D.
Indiana University

RESEARCH TRAINING

Mr. FLOOD. What legislative authority do you have at NIH to support research training other than the authority provided in Public Law 93–348?

Dr. LAMONT-HAVERS. That new piece of legislation, in effect, did away with practically all of the other authority that we had except for some within the Cancer Institute and a little bit within the Heart Institute. But, to all intents and purposes, as far as biomedical research training is concerned, we will be going with this new authority.

Mr. FLOOD. How many of these National Research Service Awards will NIH be able to make under this budget we are talking about?

Dr. LAMONT-HAVERS. In fiscal year 1976?

Mr. FLOOD. In this budget, the one in front of us.

Dr. LAMONT-HAVERS. We estimate that we will be making approximately 746 fellowships under that program next year, new awards.

Mr. FLOOD. Will the emphasis be on predoctoral or postdoctoral support?

Dr. LAMONT-HAVERS. This year, in fiscal year 1975, we will make both predoctoral and postdoctoral awards.

Mr. FLOOD. I know that.

Where will the emphasis be?

Dr. LAMONT-HAVERS. We will emphasize postdoctoral.

Mr. FLOOD. Why? Is it more productive than the other one?

Dr. LAMONT-HAVERS. As we look at the future manpower needs throughout the country, we certainly see a need to make sure there is an adequate number of people in the predoctoral pipeline but as far as the fellowships are concerned we need to focus them primarily on postdoctoral training. The predoctorals will be primarily supported by institutional awards.

Mr. FLOOD. Why the postdoctoral? Why the emphasis on postdoctoral? Why more?

Dr. LAMONT-HAVERS. It is the philosophy, I think, that by the time the individual receives——

Mr. FLOOD. Is it more productive?

Dr. LAMONT-HAVERS. We feel there is a greater need to support postdoctorals at that period in their experience and their training. The predoctorals can probably be supported in some other ways, although we do feel that there is a need to support them.

Mr. FLOOD. You know all during these hearings, whenever we ask the witness, and we have asked them all, how are these future predoctoral researchers going to be trained in the future, how are you going to finance that if we approve the budget, and they always respond that these programs can go to the Office of Education, and so forth.

Can you take us through the annual expense which is incurred in predoctoral research, that is, for the predoctoral research student in the process of his education, and show us how the Office of Education will help support that student? We have been listening to that all week.

Dr. LAMONT-HAVERS. Mr. Chairman, I heard the explanation which was given by Dr. Cooper on Monday.

Mr. FLOOD. So did I.

Dr. LAMONT-HAVERS. I cannot respond directly to your question, and I would like, if I may, to submit something for the record on that, because I just don't know.

Mr. FLOOD. OK, suppose you do that.

[The information follows:]

Cost of Predoctoral Research Training Provided by the NIH

Per trainee (data from fiscal year 1971 through 1973):	
Stipend	$3,900
Tuition	2,000
Institutional allowance	2,000
Travel	100
Per year	8,000
Average length of training—5 years or $40,000	

OE Student Assistance Available to Biomedical Predoctoral Students

Guaranteed student loans:	
Maximum per year	$2,500
Maximum total (including undergraduate borrowing) for graduate students	10,000
National direct student loans:	
Maximum total (including undergraduate borrowing) for graduate students	10,000
College work-study program:	
Under graduate or graduate students $3.50 per hour maximum for graduate students.	

Mr. MILLER. Before we leave that, Mr. Chairman, our explanation of why we have concentrated on a limited area of Federal support has not been directed solely toward the fact that support is available from the Office of Education.

Mr. FLOOD. But I am talking about that part of it, Office of Education, Office of Education, you have heard that all week.

Mr. MILLER. I would simply point out that there are other components of the reason for that policy. If you don't want us to go into them, that is fine.

Mr. FLOOD. What about the Office of Education?

Mr. MILLER. As Dr. Lamont-Havers says, we will submit the details of the answer to that question for the record.

Mr. FLOOD. Let's nail that one down. In regard to the general research support grants, that is the GRS, this committee in its report for the 1975 appropriation bill directed—and here we are, oh, boy, the Appropriations Committee of the House—NIH to reconsider that GRS formula, the guidelines by which these funds are awarded. We asked for a report on this subject prior to these 1976 hearings, and to this date we have not received the report.

Here you are flying in the face of the gods. Why?

Dr. LAMONT-HAVERS. The report has been worked on by NIH.

Mr. FLOOD. I am sure of that.

Dr. LAMONT-HAVERS. I have just received a note saying that it is going up today.

Mr. FLOOD. Going up where?

Dr. LAMONT-HAVERS. I assume up to you, sir.

Mr. FLOOD. That is nice.

Mr. MILLER. That is right, Mr. Chairman.

Dr. LAMONT-HAVERS. I am not quite sure where it has been since it left us.

Mr. FLOOD. Can you imagine that? We make a big deal out of this because of our experience, because of our problems, because of all of our conversations. Everybody sat down last year asking for this report. Everybody shook their heads saying this is a good idea. We have got to have this before 1976. Oh, yes, absolutely. We understand why you have to have it up there. Yet we have no report.

We will get it in time? You are going to be sure the report gets here about the time the hearings are over? That is about it.

Anyhow, this budget proposes to eliminate once again general research support grants. Will you explain to the committee how you reached that decision?

Dr. LAMONT-HAVERS. In the light of the budget which is being proposed for biomedical research, some priority judgments have to be made. It is the judgment of NIH that, in order to protect as much as possible the individual research projects in the research grant area, we would put a lower priority on the general research support type of grant.

SMALL RESEARCH ORGANIZATIONS

Mr. FLOOD. Isn't there a need to strengthen some of these smaller research organizations? Also give some of our research centers the opportunity to exercise onsite judgment in order that they can respond more effectively and more quickly to emerging opportunities and unpredictable requirements.

Dr. LAMONT-HAVERS. There is no doubt, sir, that that concern was one of the reasons why the general research support grant was set up in the first place. I do feel, however, at this time in our history when we are, indeed, having major economic problems, that we must look more carefully at our priorities, that perhaps the need for institutions to have broader flexibility in the use of funds is not as necessary.

Mr. FLOOD. Whoever that long-haired, flat-heeled-type downtown was who gave birth to that phrase about 6 or 8 years ago, "realinement of priorities," he certainly gave you something to latch on to.

Dr. LAMONT-HAVERS. I would point out that we are continuing one of the programs under the general authority for GRS. That is the minority biomedical research support program. That we are continuing.

INDIRECT COSTS

Mr. FLOOD. Good. Don't forget this is the Appropriations Committee you are appearing before. This is not some joint conference committee or something or other. We have a surveys and investigations staff of the Appropriations Committee. These are pros. These people have been around. That is why they are there. They conducted a study of the HEW, the indirect cost reimbursements to grantees and contractors. We had them do this. One of the significant items in that report is the fact that a larger share of the dollar that we appropriate for research grants goes into reimbursement for indirect costs. The report shows that in 1970, 22.7 percent of the dollars obligated went to pay indirect costs; and in 1974, 26 percent went to pay indirect costs.

What are you doing to control this upward spiral in the rate of indirect costs, indirect costs, indirect costs?

Dr. LAMONT-HAVERS. Mr. Chairman, in the first place, I think that indirect costs are obviously a legitimate charge to research. It is in that way that the institutions get reimbursement for the heat, light, and maintenance of the whole organization without which the research itself couldn't take place. There is no doubt that they also have been struck by the inflation spiral which has hit everybody else. That is certainly reflected in their salaries, costs of fuel, et cetera.

Many of the institutions are complaining of the fact that the indirect cost reimbursement does not indeed cover them for those costs.

At one time NIH and HEW had a fixed indirect cost rate which did not compensate the institution for everything. I think it was a decision by Congress that the indirect costs should be commensurate with the actual costs to the insitutions. The only condition was that there be a small amount of cost sharing. The increase in the indirect costs is attributable, by and large, to economic factors affecting the country as a whole.

Mr. FLOOD. We keep hearing about the need, the need for more research, and then we discover that more and more of the money that we appropriate supports indirect costs.

Dr. LAMONT-HAVERS. That is right.

Mr. FLOOD. Does that concern you as much as it does this committee?

Dr. LAMONT-HAVERS. It certainly concerns us when one looks at the amount of funds which are going to support the direct costs of the research. But we have to remember that without the indirect cost reimbursements the institutions would simply not be able to carry on the research itself.

COMMUNICATION OF RESEARCH FINDINGS

Mr. FLOOD. In your opening statement, Doctor, you mentioned the NIH effort to communicate research findings to the practicing physicians.

Dr. LAMONT-HAVERS. Yes, sir.

Mr. FLOOD. You mentioned that on the RMP's.

Will you tell us a few of the diagnostic treatment techniques developed by NIH in just the last few years which are now routinely used by practicing physicians?

Dr. LAMONT-HAVERS. Let me ask Dr. Stetten while I gather my thoughts.

Dr. STETTEN. New techniques include development, in the last few years, of an agent derived, of all unlikely places, from the blood of the horseshoe crab.

Mr. FLOOD. On nerves you mean?

Dr. STETTEN. No; this agent has turned out to be by all odds the most sensitive detecting device for the measurement of something called endotoxin, which is produced by many bacteria, which contaminates or has, in the past, contaminated commercially available intravenous fluids, and which appear in the spinal fluid in certain forms of meningitis.

This I mention, because it has intrigued some of us as an unlikely origin of a piece of research leading to a very immediately practical, useful conclusion.

Mr. FLOOD. You mean very close examination of veins as such?

Dr. STETTEN. The original observation, sir, was that the horseshoe crabs around Long Island Sound were dying in unusual numbers, and this caused someone, whose name I cannot recall, to inquire into the cause of death. He found that the cells of the horseshoe crab's blue blood were agglutinating, and he isolated from these cells a material which reacted with the endotoxins generated by bacteria that were being poured into Long Island Sound from the sewage of the adjacent communities.

Mr. FLOOD. Now that you have had a time to catch up, the question was just a few of the diagnostic techniques and the treatment techniques developed by NIH in just the last few years that are now routinely used by the practicing physicians.

Dr. LAMONT-HAVERS. Although I am sure that we can supply a greater list and that each of the Institute Directors will give further examples, let me just mention a few.

There is the test for the rheumatoid factor which is an immunological aspect which appears in rheumatoid arthritis which is now common as a diagnostic tool, not only in that disease by modifications of it have been used in other areas.

In the area of cancer we have a number of techniques all the way from mammography utilized in breast cancer to cytology techniques in other types of cancer. The detection of modifications in the enzyme levels in the blood which monitors, and being able to use the diagnostic and monitoring test for coronary heart disease is relatively new.

In diabetes we have got the advent of the test for glucogon which is an antagonist for insulin which is very useful in diagnosis ad monitoring treatment. That immediately comes to mind.

I think we can offer you a much longer list for the record.

Mr. FLOOD. That are now being routinely used?

Dr. LAMONT-HAVERS. That are now being routinely used.

Mr. FLOOD. Please submit such a list for the record.

[Clerk's note: The Department was unable to supply the information.]

Mr. FLOOD. Mr. Michel?

Mr. MICHEL. Following up on that particular line of questioning, Doctor, isn't that in part what your general statement says here, or do we sense that there is going to be a change of direction?

Your impressionistic figure is one that 80 percent of what is going on is scientist to scientist. You get down to the end line, it is only 5 percent communication between NIH and what we are dealing with on an every day-to-day basis.

Is that far fetched?

Dr. LAMONT-HAVERS. No. Basically, the fact is that the discovery of new knowledge, either in biomedicine or anything else, is a long process.

In the biological sciences there is a great deal of fundamental knowledge of which we are absolutely ignorant. We have to develop such knowledge before we can make any real progress on many disease problems.

Moreover, before one starts trials on human subjects, either individual or in groups, so that you can pass the information to the health care delivery system, you have to make absolutely sure of what you have got. You cannot use human beings as experimental animals for obtaining new knowledge in basic work.

CONTRACTING WORK OUT

Mr. MICHEL. The chairman asked for some personnel charts by institute to be inserted in the record, and the thought just occurred to me that while that might very well be interesting information for us to have, is there a direct correlation between the figures of personnel in a given institute and the amount of personnel that would also be involved by way of grant or contract to that particular institute?

You know in other departments of government, it is no secret that, well, to avoid the criticism of the Congress by asking for new additional personnel we will just contract out, and they will accept those contracts up there on the Hill very easily. You find on close examination that what they were really doing, in a sense, was getting around the personnel ceiling or some such thing by contracting the work out.

Admittedly, in some cases it is to the Government's interest because we are not obliged for a long-term personnel payment, retirement, et cetera. You just can't say contracts are all bad; you circumvented the will of the Congress by taking that route. There are arguments pro and con.

I just wondered, in keeping with the table that will be submitted, is there any direct relationship between the number of people involved in a given institute and the amount of contract or grant award that would also involve additional people?

Dr. LAMONT-HAVERS. Mr. Michel, as far as the research grants are concerned, all of the individuals involved in the administration of the program are employees of NIH—apart from the advisers in our study sections and so forth, as is well known to the Congress.

In the rest of NIH we do have certain contract programs. The contract program in the Cancer Institute to run the Frederick lab is well known to Congress, and they have other contract activities.

We are experiencing difficulties in the Clinical Center and we have had to contract out the employee health service, and to obtain the necessary expertise in anesthesiology needed by the Clinical Center. We just can't hire people under Government salaries, and that service has to be contracted out. There is no other way. It is an absolutely essential service but you can't find anybody to come on board at the salary we can pay.

Therefore we are going to have to contract. There is no way we can do it otherwise.

Mr. MICHEL. Feel free to expand a little on that point in the record, because it is an important thing. These are the personal prejudices of Members of Congress, because of the current salary limitation imposed upon Members of Congress.

We are not going to raise the judiciary, because we are not going to pay them any more than we do ourselves. We find ourselves in this kind of a situation with an eminent scientist, very qualified, wonderful professionals who in the private sector can get double and triple

what they can get in Government, and there is no way you are going to get them into this stream of things to produce for Government except through the mechanism you just described.

Dr. LAMONT-HAVERS. That is right.

Mr. MICHEL. Of course we have got some of then who are willing to write in, by way of an amendment, that under no circumstances in the contracts should anybody benefiting from the contract get a salary in excess of some arbitrary figure. We did it in education. We may very well be moving in that direction with health. All it is doing is satisfying the personal pique of a Member of Congress, but it isn't getting the job done.

I think that is the thing we have got to have spelled out very clearly in the record. There is just no way of getting around it. If you want quality, you have got to pay for it, and if you want two bits worth, that is the kind of quality you are going to get.

On the issue of fellowships and giving that priority to postdoctoral rather than predoctoral, I look at it this way. With what resources are available in the private sector, whether it is from Government or just an individual's own initiative, if one is able, through whatever help and assistance he can get, with or without Government, and he has the kind of dedication and motivation that makes him a prime target then to attract to your institute and to contribute something to the national good, then it seems to me it is a function of the National Institute of Health, after they have gone through all those tests on a personal basis, to reward that person with a postdoctoral fellowship or grant, if it is the national good that is going to benefit from it.

There are those who will argue about how you find the resources to climb up the ladder. My view is, if you have it, the determination and motivation, then where there is a will, there is a way.

The good, the bright and superlative people you are interested in recruiting are going to get to the top more, because they have more inside than any assistance the Federal Government is going to pile on them.

Finally, after having exhibited that much, to me, it makes more sense to develop that as a national resource. Then that is a Federal obligation and at that point, I cannot argue with the switch in priorities, if that is what it is.

Maybe if that is not the right moniker these days, a realinement of priorities, what is wrong with a change of direction?

If I thought my thinking today had to be the same as it was 15 or 20 years ago, God help the country and everything else.

If I have not learned something from the experience of 2 years ago to change direction in some areas in which I'm going, then I think you have a legitimate right to make the point. What we thought was a right direction 2, 3, 5 or 10 years ago has been adjusted. We are learning more, and we are going another direction and rightly so.

INDIRECT COST REIMBURSEMENT

On the issue of indirect cost reimbursement, a few years ago, we had a 15 or 20 percent limit?

Dr. LAMONT-HAVER. Yes, sir, it started with 8 percent. At that point, when that was a fixed amount, the institutions came in and made

a very effective plea that they just could not operate with that amount of reimbursement.

Mr. MICHEL. If we were to again impose some lid on indirect costs, would that tend to dry up the applications or at least inhibit the kind of applications we would receive?

Dr. LAMONT-HAVER. I'm not sure.

I don't know what the adjustment would be. I know that there would be a tremendous outcry in the institutions. But what would actually happen if a fixed level were set, I really do not know. I could guess, mainly on the basis that people have a habit of adjusting somehow.

Mr. MICHEL. It is natural for the institutions to argue that point of view. By the same token, you know it is like Federal projects, or having established the Capital in the city of Washington and then making payments to the citizens of the District of Columbia. Other cities around the country can say, "You give me the Nation's Capital, and we will pay you to come there as a result of what is generated."

I can come back to the research grants to the institutions.

It is one thing to say, "Well, we are doing it only in the name of research." You and I know that it has frankly proven to be a mechanism for the Federal Government to legitimately subsidize every medical school and dental school, with the exception of maybe one or two in the country, through this research mechanism.

Mr. SCHWARTZ. Mr. Michel, I might add that in developing these indirect cost rates, there is a fairly well prescribed standard, in OMB Circular A–21, that does attempt to approximate as closely as possible, the actual cost incurred by the institutions. We do have a very good program of audit to insure that the standards are being applied.

Mr. MICHEL. Is that variable between institutions or is it just a fixed cost?

Mr. SCHWARTZ. No, sir. It is variable depending upon the type of accounting system the institution has and the method of management.

Mr. MICHEL. Has it been adjusted upward to account for inflation in the last couple of years?

Mr. SCHWARTZ. The trend clearly has been an upward movement based upon two factors: one is inflation, the other is that many institutions are doing a better job of cost accounting.

Mr. MILLER. I think I am correct, and if I am not, Mr. Schwartz will correct me; I do not think there has ever been a legislatively imposed ceiling or a flat ceiling. The calculation of cost rate has had to do with a particular institution. There have been provisions in the appropriation bill which have said such things and I think it is still in the appropriation bill; there must be cost sharing on the part of the institution.

But it is not prescribed as a specific amount.

Mr. MICHEL. But I am reminded by our staff that when I first came aboard umpteen years ago, in this subcommittee, we did have a flat 15 percent.

Dr. LAMONT-HAVERS. You are right. In training grants we still have 8 percent. That is not legislatively imposed.

Mr. MICHEL. Well, it was a limitation on an appropriation bill

which we say you do not legislate on an appropriation bill but it qualifies as a limitation. Well, indirectly it is legislative.

FOREIGN BIOMEDICAL RESEARCH INVESTMENTS

You state, Doctor, in your closing paragraph, that "This budget continues to represent a major investment in biomedical research on a scale that no other country even attempts."

Could you expand a little on that statement, for example, in comparison with what kind of programs you find in other countries?

Dr. LAMONT-HAVERS. The only other countries that have the scope of biomedical research—covering or trying to cover virtually all the areas covered in this country—would be the U.S.S.R. and possibly Japan. Goodness knows what is happening in China.

In the U.S.S.R. both the sophistication and the extent and the depth of such research is limited. Japan does have a very sophisticated biomedical research community but obviously they are not spending nearly the amounts this country has put into it.

In terms of percentage of gross national product the picture is somewhat different but this is very difficult to measure because of the differences in size. Such countries as Great Britain and Sweden and the other Western European countries have extremely excellent scientists and very sophisticated programs, but their programs do not have the extreme breadths we do. They tend to concentrate on certain given areas.

Mr. MICHEL. I have not attended the World Health Assembly for several years now, and I will regret that. But do you know offhand of the countries you have mentioned—the Soviet Union and Japan—whether their emphasis, priorities, or whatever you may wish to call it, are pretty similar to ours so far as the individual institutes? Is heart disease, for example, as big a problem?

I would think it is a problem in the other countries, as it is here; and cancer, too. Do they pretty closely parallel our own mechanism for determining those priorities?

Dr. LAMONT-HAVERS. I don't know how they determine their priorities. It seems that their priorities are the same. Certainly, as far as the Soviet Union if concerned, cancer is a big problem. That is where a large amount of their resources go, followed by heart and then the others come after that.

The same is more or less true with Japan. Certainly cancer seems to be a problem of major concern to all of the Western countries that I am aware of, and heart disease, also.

Mr. MICHEL. Is there more tying together and more sharing of information on cancer than anything else, would you say?

Dr. LAMONT-HAVERS. I do not know about anything else, but certainly the international cooperative programs in cancer are great. I am sure Dr. Rauscher will speak to that because this is a major program in his area.

I might say that with the U.S.S.R–U.S. cooperative program in health, we are now beginning to find out what is happening.

Mr. MICHEL. Please feel free in the record to expand if you have any specific expenditure levels vis-a-vis compared with gross national product. We would like to have them.

[The information follows:]

Insert 3108 A

LEVEL OF MEDICAL RESEARCH ACTIVITY ABROAD

Most foreign governments do not publish statistics on the amount of support being provided to biomedical research within their country. Financial figures relating to research support by communist governments have not been published as a result of government policy. Many non-communist governments do not have such figures available for a variety of reasons. Among those governments which do, the published statistics usually refer only to the principal supporters of biomedical research, such as a Medical Research Council, and do not include biomedical research support by other national agencies, state or municipal governments, the industrial sector, including pharmaceutical firms or voluntary organizations. As far as we know, reasonably complete figures are available only for the United States, Sweden, the Federal Republic of Germany, and India. For Italy and Japan, figures are available only for support provided by the national government but not for provincial/prefectoral or private sector support. The remaining figures in the following table (U.K. through New Zealand) refer only to their *Medical Research Council* or, in the case of France, to the *National Institute for Health & Medical Research*. No information is available on how the funds are distributed between the major disease categories.

Country	Medical Research Support Year	($ million)	GNP-1973 ($ billion)	Population Mid-1972 (millions)
TOTAL SUPPORT				
United States	1973	$3,563.0	$1,289.1	208.8
Sweden	1974	83.5	48.6	8.1
Germany (F.R.)	1973	69.6	319.7	61.7
India	1975	10.0	58.3*	563.5
NATIONAL GOVERNMENT ONLY				
Italy	1974	71.0	142.8	54.3
Japan	1972	67.8	412.0	107.0
MEDICAL RESEARCH COUNCIL ONLY				
United Kingdom	1973	64.1	171.1	55.8
France	1973	53.7	247.6	51.7
Canada	1973	36.8	117.5	21.8
Israel	1972	7.0	6.9*	3.1
South Africa	1973	5.8	21.0*	23.0
New Zealand	1973	2.3	9.0*	2.9

*in 1972

Mr. MICHEL. I will have several questions which I will insert for the record along this line in the international field.

EXPENDITURES FOR COMMUNICATION ACTIVITIES

Mr. MICHEL. How many people do we actually have involved in your shop, involved in dissemination of information? Is that broken out in any block amount?

Mr. SCHWARTZ. We have a central unit for communication that consists of about 30 people. Then each Institute will have one or two people involved in communication with the public. We also have groups of technical information specialists.

That probably amounts to a total, for NIH, of about 150 people.

Mr. MICHEL. You have an expenditure aggregating at roughly what?

Mr. SCHWARTZ. As Dr. Lamont-Havers has mentioned, research information communications activities are integrated into almost every program of the NIH. It is therefore quite difficult to estimate the true cost of such activities.

However, in addition to the National Library of Medicine, the basic mission of which is scientific communications, we are able to identify NIH expenditures during 1975 for informational activities including scientific and technical communications which total approximately $2,335,000 for personnel and $2,662,000 for publication costs.

SUPPORT FOR MEDICAL RESEARCH AND TRAINING

Mr. MICHEL. Last year I asked that a table be updated in the record showing the growth rates of national support for medical and health-related research and training, showing the source of funds by Federal and non-Federal areas. I would like to have that table updated for the record this year if I might.

Insert 3111 A

National Support for Medical and Health Related Research and Development,

by Source of Support, 1947-1974[1/]

(millions of dollars)

Year	Total	Federal	Non-Federal						
			Total	State and Local	Industry	Foundations & Health Agencies	Other Private Contributions	Endowment	Institutions Own Funds
1974	$4,291	$2,795	$1,496	$92	$1,180	$136	$34	$19	$35
1973	3,507	2,206	1,301	80	1,018	116	33	19	35
1972	3,352	2,145	1,207	79	925	116	33	19	35
1971	3,002	1,857	1,145	78	860	120	33	19	35
1970	2,728	1,664	1,064	76	795	108	32	19	34
1969	2,672	1,656	1,016	72	754	108	32	19	31
1968	2,486	1,571	915	69	661	106	30	19	30
1967	2,281	1,459	822	65	580	100	29	19	29
1966	2,053	1,316	737	61	510	91	28	19	28
1965	1,837	1,174	663	55	450	88	25	19	26
1964	1,652	1,049	603	50	400	88	22	19	24
1963	1,486	919	567	45	375	85	21	19	22
1962	1,290	782	508	37	336	78	18	19	20
1961	1,045	574	471	30	312	77	15	19	18
1960	845	448	397	23	253	76	12	19	14
1955	261	139	122	5	62	31	1	16	7
1950	161	73	88	-	51	21	N.A.	14	2
1947	87	27	60	N.A.	35	15	N.A.	10	N.A.

1/ Coverage is limited to conduct of research and development. Support of other activities such as research training or capital outlays for research facilities are not included.

Mr. MICHEL. What input have private sources made into the problems?

Last year's statistics indicated that foundations and private organizations have not increased their support significantly over the last 4 or 5 years while Federal support for these activities have increased in a striking amount.

What percentage of support does come from non-Federal sources for the kind of work in which you are engaged?

Dr. LAMONT-HAVERS. NIH supports about 40 percent of the biomedical research. Other Federal support is about 25 percent. So therefore a total of about 35 percent comes from non-Federal sources.

Mr. MICHEL. In this budget for 1976, what percentage of the research would be done in-house as distinguished from that by grant and contract award?

Dr. LAMONT-HAVERS. Only 10 percent of the budget will be spent for the intramural programs.

AVERAGE LIFE OF A RESEARCH GRANT

Mr. MICHEL. What is the average life of the grants?

Dr. LAMONT-HAVERS. The average grant now runs for about 3.2 or 3.3 years.

Mr. MICHEL. Renewable or subject to review on a yearly basis or what?

Dr. LAMONT-HAVERS. If they are 3-year grants, they have to come in for complete review during the third year, before renewal just as if they were a new grant application.

Mr. MICHEL. But once awarded for a period of 3 years, that is pretty well established?

Dr. LAMONT-HAVERS. We do not do intensive annual reviews. That would not be feasible. The investigator has to gear up for a year and after he has had it geared up for a year, then he already has to start developing his new application, if he wants to continue.

Mr. MICHEL. For the sake of the record—I know—but even though it is a 3-year grant, cranked into the 1976 budget is only the amount of obligation you have for one-third of that grant award payable in 1976?

Dr. LAMONT-HAVERS. That is quite true. We make it in yearly instalments.

Mr. MICHEL. Basically, what happens to an ongoing grant in a particular field if there is suddenly a major breakthrough or perhaps even the answer to a given line of research?

Dr. LAMONT-HAVERS. That illustrates the greatest differences between grants and contracts. A contract clearly specifies what you want that individual to do. A grant, however, is given to an individual to pursue a general line of work. Obviously if there is a breakthrough, he would automatically follow that up. There is only rarely an end to a chain of research. There are almost always further questions that need to be pursued.

Mr. MICHEL. Do you ever have an occasion where you award a grant to discover a cure for disease X, and another grantee comes up with a solution before the completion of the grant for which you were looking for the answer?

In that case what do you do then?

Dr. LAMONT-HAVERS. In the nature of science, it is a fact that we would not only hope that that would happen, but I'm sure that it does happen. That is the nature of the game. We are really supporting prepared minds. Sometimes—quite often really—they come up with an idea that may not have anything to do with what they thought they were looking for.

Mr. MICHEL. I have some additional questions which I will ask after the other members of the committee have had a chance to question the witness.

Mr. FLOOD. Mr. Natcher.

ESTABLISHING BUDGET PRIORITIES

Mr. NATCHER. Doctor, as you point out in your statement, the amount requested for the National Institutes of Health is $1,800,000,000. It is a large sum of money. I am just wondering now how you arrive at the amounts for the different national institutes. We now have 11 institutes.

Dr. LAMONT-HAVERS. That is correct.

Mr. NATCHER. During the last 3 years we have added two new ones. How do you establish your priorities as far as cancer, heart, and strokes are concerned? As far as your other institutes are concerned, the $1,800,000,000 is a large amount of money, of course. When the Secretary appeared before our committee he talked somewhat about the cost for defense, and we always discuss that with him when certain reductions are made. For several years, for some reason or other, he cited the need for tremendous amounts for defense. I know the members on this subcommittee believe that this is a real important bill and know that we have $36,700,000,000 in new obligational authority. Mr. Miller and I talk from time to time about new money and I know that this overall bill probably deals with $114 billion, but it is social security trust money, railroad retirement, and other funds in addition to new money; $1,800,000,000, Doctor, is a lot of money, but from the standpoint of need and from the standpoint of this being the people's department, it is not a lot of money. I think you would agree with that.

How do you establish your priorities?

Dr. LAMONT-HAVERS. As the budget is being developed we obviously look primarily at our commitments. That takes up a considerable portion of any budget. Then we look at the amount available above that. That amount usually is relatively small.

For instance, in a budget of approximately $2 billion, we might have $300 million which we can allocate. In considering the factors going into that allocation, we look first at the national priorities that have been established both by the Congress and by the executive—such as the cancer and the heart and lung programs. Obviously, we feel that their momentum should be kept going, as much as possible, at the level determined by Congress and the executive branch.

The next things we consider are the legislative mandates or priorities which have been set through congressional hearings. This year this included such things as arthritis, a new diabetes bill, an interest in the sudden infant death syndrome, multiple sclerosis. There is quite

a list. So we feel we have to give priority to distribution of funds to those areas.

Then we look at the need to support the production of new knowledge that is really not related to any specific categorical interest. We distribute the money to the Institutes as we feel that they can best employ it within the total amount available.

It is in these general ways then that we consider how to set our priorities. I would like to stress the fact that the amount of money that is so distributed is relatively small in comparison to the total budget in any 1 year.

RESPONDING TO CRITICS

Mr. NATCHER. Doctor, I know from time to time that you as the Acting Director must receive complaints concerning amounts that are recommended to the Congress for the National Institutes of Health. Only recently I know that one of the doctors, a Dr. James Watson, made certain observations which Dr. Rauscher, I believe, answered concerning the amounts and results that we have so far for cancer. Now when you have these complaints as to the amounts and so forth, generally instead of just disagreeing, what do you do about it, Doctor? When a statement is made that the Government's newly created cancer research centers around the country are institutions that are starting out lousy and will stay lousy, and further that the national cancer program is a fraud. What do you do about it, Doctor?

Dr. LAMONT-HAVERS. I either do nothing or I answer in the given media.

Mr. NATCHER. We are concerned. What about the money, procedure and your budget for cancer.

Dr. LAMONT-HAVERS. I think Dr. Rauscher and the Cancer Institute have given a very excellent defense of their budget. At NIH we have absolute confidence in the scientific merit of the material being produced.

In my own thinking and in my discussion of this problem I look back on history. Most of these critics are looking at the fact that it is 3 years since the latest cancer plan was initiated and that we have not conquered cancer.

Mr. NATCHER. You are talking about the 1971 increase?

Dr. LAMONT-HAVERS. Right, but one has to go back in history and look at the concerns of this Nation in the late 1920's which led to the establishment of the National Institute of Health, to the establishment of the National Cancer Institute in 1937, and then to the other categorical Institutes the other diseases during the next decade.

Now we are coming into a new era of biomedical support again led by the demand of our society for increased emphasis in overcoming cancer. It is the historical pattern and one has to put it into proper historical perspective. I don't see this as a great, terrible thing, or as science being undermined, or as anything else sinister. It is the natural evolutionary process. It will straighten itself out in a year or 2 and we will get back to a proper alinement.

BASIC RESEARCH AND/OR CRASH PROGRAMS

Mr. NATCHER. Doctor, some people in the medical profession who are very much concerned about your program and about research

generally say that if we had a crash program of $10 or $20 billion as far as cancer is concerned, it might not prove successful as far as a solution is concerned and instead of crash programs we ought to have more basic research. Maybe the word "basic" is not correct. What do they have in mind?

Dr. LAMONT-HAVERS. I think what they have in mind is the fact that the production of new knowledge, which will eventually lead to the betterment of the health of the citizens of this Nation, does not usually come from concentrating on a particular disease. It comes from an understanding of the basic biological mechanisms in man. That understanding gradually becomes adapted and directed toward specific disease entities. The fact is that we do not have sufficient knowledge of those fundamental biological mechanisms going on within man and his diseases. Many people feel that this broad base should be supported, research such as we now support in the Arthritis Institute, the Neurology Institute, and the Institute for General Medical Sciences and that, eventually, the new knowledge we will come up with will be effective for cancer and many other diseases. However, this is not a perfect world. We have in this country, in our political system, the involvement of the citizens of this country in determining what should be done with their tax dollars. They have determined, through whatever process, that approximately one-third of the budget of NIH should be in the Cancer Institute. If that is their determination, that is what will happen.

I think we can use that money effectively. It could be distributed many other ways. There is no doubt about that. I imagine every scientist would have a different view as to how he feels that money should be distributed.

Mr. NATCHER. As you well know, Doctor, when Members of Congress on the floor of the House and Senate discuss generally the dread diseases they make speeches as to the number of deaths last year and the need for billions of dollars in crash programs. It is real easy for the parade to start and all of them try to carry the banner and get up at the front of the parade. But as a doctor and one who is qualified to serve in your position, would you say to me or agree with me that as far as crash programs generally maybe you are not traveling the right road.

Dr. LAMONT-HAVERS. Generally cash programs indicate that you have the fundamental knowledge with which to immediately proceed. Generally, we do not have that for most of the conditions to which the mission of the NIH is directed.

Mr. NATCHER. You see the position that Members of Congress are in when they start these moves from other committees and in the House generally. It puts you in a position of not knowing whether or not your money is going to be well invested.

As far as cancer, heart, and stroke is concerned if $5 billion would do the job, I would vote for it.

Dr. LAMONT-HAVERS. If I thought that $5 billion this year would immediately eradicate cancer from the Nation it would be well worth spending. But I do not have that confidence.

Mr. NATCHER. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Patten.

LEVEL OF SUPPORT

Mr. PATTEN. Put the 5-minute clock on me, Mr. Chairman, because I think the Acting Director, Dr. Lamont-Havers, can easily understand how some of us can get enthused listening to him. We share your pride in NIH. I think your statements are valid. I think it was a redheaded doctor who came here a few years ago. He spoke of genetics and the DNA factor and how in the next 10 years probably we would save more life years than we had in the whole history of mankind through breakthroughs in sickle-cell anemia and everything else. I went out of here on a cloud, I felt so happy. Of course, the chairman asked you to try to put a dollar price on it. We eliminated polio, diphtheria, scarlet fever, measles.

He went right down the line on what had been accomplished in your biomedical work and it was a real pleasure. But you just told me that the overall reduction here is going to be 14 percent in real terms.

If you include the inflationary factor it is maybe a 20 percent cut in real money. As a politician, I can tell you that my people at Princeton and Rutgers University are very seriously worried about your grants and fellowships. They think they are doing a good job.

GENERAL RESEARCH AND TRAINING

Just think of the general research support. We think we are doing a swell job with the few dollars you are giving us. But not only that, we are training a leadership for other schools in the alcohol program, that you have cut. I think we are accomplishing something. I know we have 300 people working in the ghettoes with the alcohol money. Our county college is brand new and your statements in 1970 were that we needed 1 million paramedicals. The Federal Building we put up in the Community College has a lot of dental chairs. They train people to help dentists. They have taken a lot of the responsibility away from our poor hospitals that were always burdened with nurses training programs.

At the county college they were giving nurses postgraduate work. I know the people in the work were very happy. As I read this program I am just wondering about the nursing research training grants and the fellowships administered by NIH; I don't see them in the budget. Did I miss them?

Dr. LAMONT-HAVERS. The nurses' research and training is not the responsibility of the NIH.

Mr. PATTEN. But NIH has something to do with it.

Dr. LAMONT-HAVER. It used to be there about 4 years ago when we had the Bureau of Health Manpower. That has become part of the Health Resources Administration. I'm afraid you will have to wait until Dr. Endicott comes up.

Mr. PATTEN. How much has been budgeted for training grants and fellowships? The truth is that none has been.

We put in money for ambulatory patients. Is it in my head that OMB held up the money. What is the status of that?

Mr. SCHWARTZ. Mr. Patten, we received a $3 billion appropriation for the design of the ambulatory care facility.

These funds have been released. We have awarded the contract and currently are underway with the design.

INTERMURAL RESEARCH PERSONNEL PROBLEM

Dr. LAMONT-HAVERS. There is a problem, within NIH generally but certainly within the intramural program, with regard to the salary levels particularly as it affects our senior individuals who indeed can go out and get better salaries elsewhere.

Also, as we have been trying to adjust to the reduction in personnel, we find that the numbers of technicians, of animal care personnel and of other types of ancillary personnel are decreasing while the number of professionals stays about the same. This leads to some problems with regard to productivity. There is a difficulty.

Dr. Stetten, who is primarily responsible for the intramural program might wish to comment.

Dr. STETTEN. Mr. Patten, scientists are querulous people by nature. They always find something to complain about. Their complaints usually are that they do not have enough hands, dollars or equipment or space or they have not enough freedom to operate. Always, for the aspiring scientist, one or another of these is the oppressive constraint. I think in the intramural program, at this time, it is the shortage of position slots which is at the moment most irksome. It is certainly the complaint that comes to my office most frequently. When this one is solved it is my firm belief that another will supersede it. So I am not too worried about it, but it does exist, that is right.

Mr. PATTEN. To draw an analogy, if your life was to draw up labor contracts between management and labor, of which we have thousands every year, you can easily get heart trouble. I have seen fellows who have had to negotiate a labor contract have heart attacks. That's the strain of the way they live. I am sure you will overcome these problems.

ARTHRITIS

Let me ask you, you spent 20 years of your life in this arthritis business. Do you regret it? Do you wish you had it to do over again?

Dr. LAMONT-HAVERS. Would I do it differently?

Mr. PATTEN. Twenty years ago you ran our Arthritis Institute up in New York. In your presentation here the word arthritis does not appear once. I am getting to be that age, Doctor. Don't leave us.

Dr. LAMONT-HAVERS. We are certainly not going to leave you.

We had the first meeting of the Arthritis Commission that was established by Congress through legislation. They will be submitting a report to this committee within 7 months.

Mr. PATTEN. But they are going to have $25 million less. That was cut out of fellowships and grants.

You are part of the détente with the U.S.S.R. You went over there a couple of years ago. Did you accomplish anything with them on arthritis?

Dr. LAMONT-HAVERS. Yes, sir. I was there in 1964. The difference between 1964 and 1974 is very great. I think they have come a long way. We have identified some programs on which we can start cooperation with them. The Russians are coming to see us next month in order to finalize some of those details. I think it will be a productive interchange providing one does not look for something happening next year. It will take a little while to undertand each other.

Mr. PATTEN. Mr. Chairman, we have great respect for the Director and his staff. Last year you gave us an outline on one sheet of paper. I do not see it around here today.

We referred to the many times during the year when people ask questions. Is it too fluid to put in print?

Dr. LAMONT-HAVERS. It is rather fluid. That was a gross oversight and I apologize.

I am glad you brought it up. We will make sure that oversight does not happen again.

Mr. PATTEN. Thank you.

Mr. FLOOD. Mr. Roybal.

LUNG DISEASE

Mr. ROYBAL. Doctor, reading the justifications for your budget, I see that you have new activities which have been initiated and which have significantly added to the Institutes' responsibilities. One of those is the development of an expanded program in lung disease. I would like to know how this program has been expanded. What effect has it had particularly in view of the fact that the incidence of tuberculosis has increased substantially in this Nation?

Dr. LAMONT-HAVERS. Mr. Roybal, I'm sure that Dr. Ringler, when he speaks to you tomorrow—he is the Acting Director of the Heart and Lung Institute—can give you a much more detailed explanation than I can. The great increase in the effort that NIH is putting into the diseases of the lung comes about through the heart and lung legislation which directed that not less than 15 percent of the funds allocated to that Institute should go into the area of the lung. That made the amount of funds available in this area much larger than they had been in the past.

This has led to markedly increased activities with all types of chronic lung diseases, as well as the more acute lung diseases. With regard to the specific question you ask with regard to tuberculosis, I do not know the answer, really. I would like to refer that to Dr. Ringler and have him ready or supply something for the record if you don't mind, sir.

Mr. ROYBAL. I hope you will be able to mention it to him because I would be interested in knowing the answer to that question.

Dr. LAMONT-HAVERS. Sir, he will give that to you tomorrow afternoon.

Mr. ROYBAL. And also the amount being spent for that specific item, not just a percentage. Do you have that at the moment?

Dr. LAMONT-HAVERS. Not for tuberculosis.

NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM

Mr. ROYBAL. Do you have the amount being spent for the coordination of the national high blood pressure education program?

Dr. LAMONT-HAVERS. As a matter of fact, the amount allocated directly to that is only about $2 to $3 million. For a relatively small investment, that program is doing wonders. They have done a tremendous amount with a relatively small budget primarily through working with the States and local communities, initiating the programs in those areas.

Mr. ROYBAL. Will we be able to get more detailed information as to how the local community benefits from this program tomorrow?

Dr. LAMONT-HAVERS. Yes, sir. I think the Heart and Lung Institute is very proud of that program.

INCREASE OF TUBERCULOSIS

Mr. ROYBAL. I am very interested in that. I was at one time director of health education for the National and California Tuberculosis Association. I remember that there was a high incidence of tuberculosis, so high that it was almost impossible to get anyone placed in sanitoriums. Years later, tuberculosis had practically disappeared. All of a sudden I get information from the health agencies in California that it is again increasing.

The first question that comes to mind is, if you are in fact expanding these programs, why is it that there is a significant increase?

It puzzles me, and I would like to get answers for these questions.

Dr. LAMONT-HAVERS. Yes, sir.

I will ask the Director of the Allergy and Infectious Disease Institute about that. It may be like the case of VD, where the decrease was due to social measures and also the specific antibiotics, but where there was again a subsequent increase. It may be like that in tuberculosis. I am not sure, but we will have that answer for you.

Mr. ROYBAL. Again, if I may repeat, I would like to know the amounts being spent for these specific programs.

Dr. LAMONT-HAVERS. Very good, sir.

Mr. ROYBAL. Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Stokes.

SICKLE-CELL DISEASE

Mr. STOKES. Doctor, I would like to get into some questions regarding both the sickle-cell disease program and the hypertension program. I do not know whether you are the proper person to supply me with the answers or not. Are you?

Dr. LAMONT-HAVERS. That would be Dr. Ringler who will be presenting that to you tomorrow afternoon. Both programs are in his area of responsibility. However, if there is something general, I would be happy to try to answer.

Mr. STOKES. I think I will just reserve, Mr. Chairman, if the gentleman who has responsibility will be here tomorrow.

I note at page 6 of your prepared testimony you indicate a commitment to two of these programs. You say, "to this end NIH will continue such large-scale efforts as the National High Blood Pressure Educational Program and the National Sickle Cell Disease Program." Yet in terms of your 1975 and 1976 budgetary amounts, you actually request less money for 1976 than you did for 1975; is that right?

Dr. LAMONT-HAVERS. As far as sickle cell disease, sir, there will be $16 million in 1976 and in 1975 there will also be $16 million. That, in effect, considering that the totality of the budget is less in 1976, would indicate that we are giving differential prior to that program.

Mr. STOKES. You mean by maintaining it at the same level you are giving it priority.

Dr. LAMONT-HAVERS. Yes, in order to keep it level you have to decrease others even more, if you have an overall decrease in the budget.

Mr. STOKES. Overall budget.

Dr. LAMONT-HAVERS. Yes, within that appropriation.

If one of the programs stays the same, then something else has to be decreased proportionately more.

HYPERTENSION

Mr. STOKES. What do you do with reference to your hypertension program?

Dr. LAMONT-HAVERS. That is down about $2 million, sir. That is the totality of the hypertension activities within Heart and Lung Institute, not the particular program Mr. Roybal was referring to. What happens to that program next year, I am not sure.

Mr. STOKES. It is down $2 or $3 million?

Dr. LAMONT-HAVERS. No. The particular program Mr. Roybal mentioned is the hypertension program, I am not sure what happens to this specifically. The amount I gave now is the totality of all hypertension activities within the Heart and Lung Institute which will be down about $2 million.

Mr. STOKES. In the justification figures, and you correct me if I am wrong, I show for appropriation under the Heart and Lung Institutes, 1974, $42 million; in 1975, $39 million, and in 1976, $40 million. Are those figures correct?

Dr. LAMONT-HAVERS. Which page is that sir?

Mr. STOKES. This comes from your justification report figures.

Dr. LAMONT-HAVERS. We have a different figure on different pages.

Mr. STOKES. This is page 1 under "High Blood Pressure and Hypertension."

Dr. LAMONT-HAVERS. That is the special report.

Mr. ROYBAL. Why do those figures differ?

Mr. STOKES. I am trying to ascertain.

Dr. LAMONT-HAVERS. What you want is an explanation of the activities in the special report submitted on hypertension. That you will have.

Mr. STOKES. And the amounts being expended in that area.

[The information follows:]

Budget for Hypertension

Obligations for NHLI Hypertension Programs totaled $47.4 million in 1974. Comparable figures for 1975 and 1976 are $39.5 million and $35.5 million. These figures differ somewhat from previous figures submitted in the special report on "High Blood Pressure (Hypertension)". This is the result of a recently completed review of 1974 data, which has resulted in a reevaluation of 1975 and 1976 estimates as well.

A summary of 1974 Hypertension programs follows:

Hypertension Activities	Amount (in millions)
Regular research grants	$21.0
Hypertension Education grants	1.0
Training programs	2.4
Segment of Multiple-Risk Factor Intervention Trial	5.1
Hypertension Detection and Follow-Up Program	11.1
Hypertension information contracts	0.9
Hypertension etiology and other clinical applications	0.8
Laboratory and clinical research	2.7
Research management and program services	2.4
Total	47.4

Activities in Hypertension

Hypertension is a condition resulting from a breakdown in the complex control system that maintains equilibrium between the constricting and the dilating forces of the arterial walls and the forces of the circulation. In hypertension, the normal level of balance is shifted upward so that the blood is circulated in the arteries under higher pressure. The increased pressure may damage both the blood vessels and the heart. Thus, hypertension is a risk factor for heart attack and heart failure and it is the major predisposing factor for stroke.

The evaluation of preventive measures for coronary heart disease continues to be an important challenge. Several trials are underway or in the initial recruitment and start-up stages. Their duration projects several years into the future and their findings will do much to condition medical and public health attitudes to the prevention of diseases dependent on arteriosclerosis. In the great majority of cases we currently lack the means to prevent or cure hypertension even though treatment is possible. The serious nature of hypertension, the vast numbers of persons affected, and the logistical, medical and motivational problems associated with its treatment make it essential that enough understanding be gained through research to allow its prevention or cure. At the same time, effective treatment currently exists and its use should be enhanced.

- Major long-term goals in hypertension are to understand its causes and to reduce its prevalence.

- An immediate goal is to optimize the use of currently available effective treatments.

Mr. STOKES. With that, Mr. Chairman, I would reserve any further questions for the gentleman who will appear tomorrow afternoon.

Mr. FLOOD. Mr. Shriver.

ON NOT JUDGING A BOOK BY ITS COVER

Mr. SHRIVER. Dr. Lamont-Havers, I appreciated in your statement the analysis of the various stages of research conducted with these funds. As you know, the whole question of federally-supported research projects has come into question recently because of a few badly designed, or at least badly titled projects. This is unfortunate especially in NIH, where you have accomplished so much for the better health of our people.

But sometimes even NIH-supported projects make it difficult for some of us to understand the benefits derived by the people who are paying the bills—our taxpayers. I refer again to the results announced last October 25 of research conducted by the National Institute of Child Health and Human Development. This project, which apparently stretched over about a year, supposedly proved that baby monkeys will accept mongrel dogs as substitute mothers.

I have read this release carefully—it even included a picture of a monkey clinging to a dog—and I can't find any potential help for human health problems. The main findings seem to be that the monkeys reached the point where they preferred the company of dogs rather than other monkeys, although any old dog would do. I'm not sure that is a step forward.

How much did this research cost? How many researchers were involved?

I mean this as constructive criticism. You do a lot of good at NIH. But projects like this one tend to destroy public confidence that tax dollars are being well spent.

I would suggest that when proposed research projects are being considered for funding, that more weight be put on the question of what is the benefit to be gained for the people who are paying the bills—the taxpayers.

Dr. LAMONT-HAVERS. The project to which you refer, supported by the National Institute of Child Health and Human Development, is an initial attempt to explore the feasibility of a primate/canine model in the evaluation of the attachment behaviors of children. We know from human clinical experience that separation and isolation of infants and children from their parents and home environment has profound psychological consequences upon the social, emotional, and intellectual development of children. We also know that early life experiences which prevent the development of positive affectional bonds of attachment between parents and children is the principal causative factor in the breakdown of parent/child relationships and the development of social alienation and distrust. The study of the mechanisms and underlying processes of affectional attachment becomes extremely important, if we are to acquire the basic knowledge that is required to improve the quality of parent/child relationships. The experimental study of this important social psychological area requires the use of animals, because many of these kinds of studies cannot, for ethical reasons, be conducted with children. This project

involves approximately eight full-time researchers and will cost $402,841 over the 3 years of the project.

HEALTH RESEARCH AND DEVELOPMENT

Mr. SHRIVER. You mention that support for medical research and development, from all sources, totals more than $4 billion annually in this country. Would you break that figure down by source of support for the record?

Dr. LAMONT-HAVERS. The total for Health Research and Development amounted to $4.3 billion in 1974. We will break that figure down for the record.

Agency	*Millions*
National Institutes of Health	$1,737.8
Alcohol, Drug Abuse, and Mental Health Administration	147.2
Center for Disease Control	40.6
Health Resources Administration	55.6
Health Services Administration	12.1
Food and Drug Administration	44.0
Other Agencies, Department of Health, Education, and Welfare	38.5
Atomic Energy Commission	126.5
Department of Defense	121.4
Department of Transportation	120.7
Veterans' Administration	81.1
National Aeronautics and Space Administration	80.2
Department of Agriculture	59.7
National Science Foundation	47.0
Department of Interior	33.3
Environmental Protection Agency	18.8
Department of State	10.3
Special Action Office for Drug Abuse	10.0
Department of Commerce	5.7
Consumer Products Safety Commission	4.3
Department of Justice	.5
Tennessee Valley Authority	.1
Subtotal, Federal support	2,795.5
State and local government	92.0
Private industry	1,180.0
Private nonprofit foundations	54.0
Private voluntary health agencies	82.0
Other private nonprofit	88.0
Total, health research and development	4,293.0

GETTING RESEARCH RESULTS TO PRACTITIONERS

Mr. SHRIVER. You also mention the problem of getting practicing physicians to actually use research results developed by the Institute. Most of them just don't have the time to read all the materials available. We have many citizens, however, who don't miss much when it comes to health items published in their local newspapers or announced over the broadcast media. They, in turn, can put pressure on their physicians to find out more about the subject. How widely published are the "News and Features from NIH" news releases? Could you do more of this type of news dissemination?

Dr. LAMONT-HAVERS. "News and Features from NIH" is but one of several similar information activities carried out by the NIH. This news and photo service based on research information provided by all institutes is sent biweekly to 103 metropolitan daily newspapers, 40 lay periodicals, 80 professional journals, 35 news syndicates, and 150 news writers. While we do not have statistical information on the use of such materials by the media, we frequently encounter articles derived from "News and Features" in publications like Reader's Digest, and in large newspapers. Our mailing list is purged annually and our current mailings are based on yearly evaluations.

"NIH Search for Health" a weekly column for small daily and weekly newspapers is used by about 500 such media. This service has been provided weekly for almost 10 years.

Discs and live copy are provided on a regular basis to over 2,000 radio stations on their request. The stations receive in quarterly shipments 80 health-related announcements each year.

We are now intensifying our public health education activities through the broadcast media, radio, and television. Our action plan to improve dissemination of research information from NIH includes increasing the output of health education information for use by the mass media.

Mr. SHRIVER. Thank you.

Mr. FLOOD. Mr. Michel?

IMPLEMENTATION OF RESEARCH

Mr. MICHEL. I think you addressed yourself to one of the major concerns of many of us when you discussed the problems of implementing the information developed by all this research. Along these lines and in conjunction with this problem of worldwide research, what kind of activity is involved in exchanging information on research and discovery from other countries? Are we getting the full benefit of materials available from scientists from around the world and how do we go about obtaining that kind of data?

Dr. LAMONT-HAVERS. International scientific knowledge provides continuous inputs for U.S. research. Conversely developments in the health science and U.S. research contribute significantly to the progress of research worldwide. U.S. scientists participating in the programs of NIH whether intramural or extramural, annually receive many international visiting scientists and take part in international meetings to share and exchange scientific information. Our relationships with scientists in the United Kingdom and Canada are close and productive. Formal and informal exchange of information between

scientists in the United States and many other countries occurs through publication in internationally distributed journals and books, through individual exchange of reprints and results and through international information retrieval systems like the National Library of Medicine's Medical Literature Analysis and Retrieval System (MEDLARS) and the National Cancer Institute's International Cancer Research Data Bank.

A number of multilateral and bilateral agreements between the United States and other nations involved in biomedical research provide a stable framework for intensive information exchange.

UNITED STATES-JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM

Since 1965 we have had very active participation in the United States-Japan Cooperative Medical Science Program managed by the National Institute of Allergy and Infectious Diseases (NIAID), and involving several institutes. This program covers seven disease areas and each is defined by quite specific scientific objectives. These objectives are jointly adopted by panels of United States and counterpart Japanese investigators. Each country then proceeds to pursue these common research goals according to its own initiatives and resources. Annual research conferences then provide for active scientific communication of research results and progress.

In 1974 an agreement was signed for United States-Japan cooperation in cancer research. The agreement provides for: (1) Sponsoring of selective scientific seminars to facilitate the exchange of views between American and Japanese cancer research scientists; (2) the exchange of scientists between the two countries; and (3) the promotion of exchange of materials and information.

Cooperation with the U.S.S.R. has been proceeding in a number of research areas under joint programs established through formal agreements signed in 1972 and in subsequent years.

The U.S.-U.S.S.R. Joint Program in Cardiovascular Diseases provides a direct link not previously available between the research communications in these two countries.

The program includes continuous exchanges in seven cardiovascular areas. Exchange of scientists delegations, techniques, publications, information and laboratory equipment has increased significantly since the initiation of this program. Joint publications and proceedings have been published in English and Russian in the United States and the U.S.S.R. to disseminate further the information developed during joint workshops, meetings, and symposia between United States and Soviet scientists.

Similar activities and exchanges are well established under a series of joint working agreements between the United States and U.S.S.R. devoted to cancer research. In addition to constant informal communication through exchanged scientists, six formal joint working groups of United States and U.S.S.R. scientists held working meetings in the United States and the Soviet Union during 1974.

The National Institute of Environmental Health Sciences is an active participant in the U.S.-U.S.S.R. Agreement on Cooperation in the Field of Environmental Protection. A more recent joint U.S.-U.S.S.R. agreement on research in arthritis involves the National Institute of Arthritis, Metabolism, and Digestive Diseases.

In October 1974 an agreement in cooperation in the field of health was signed by the United States and the Polish People's Republic. This agreement like the others previously cited involves communication and exchange of scientists under it. The National Cancer Institute has recently established a working relationship with the Warsaw Institute of Oncology.

The National Institute of Dental Research (NIDR) exchanges research information through the International Association for Dental Research and the Federation Dentaire Internationale and the Pan American Health Organization, a part of the World Health Organization. NIDR participates in the meetings of the above mentioned organizations. Close cooperation with the World Health Organization is maintained in dissemination of fluoridation information.

The United States-French Agreement for Scientific Cooperation provides for scientific information and personal exchanges in a number of categorical areas.

The World Health Organization and the International Agency for Cancer Research are also important channels of international communications with which the NIH is constantly involved.

The National Cancer Institute (NCI) is deeply involved in the collection and dissemination of cancer research information on an international scale as a result of the International Cancer Research Data Bank (ICRDB) progarm. The ICRDB program has established a Current Cancer Research Project Registry Office which is currently requesting descriptions of current cancer research projects from countries around the world. Contracts are currently being reviewed which will screen all major biomedical journals from many countries, select articles that deal with cancer, and prepare abstracts of the published research results.

The ICRDB program is also negotiating with organizations in Japan, South America (with the Pan American Health Organization, PAHO), Russia and other countries to set up satellite centers which will provide a steady stream of data about cancer research results in those geographic areas to the ICRDB program. Internation-

al centers for collecting worldwide information about cancer epidemiology projects and tumor immunotherapy projects are currently established and operating.

A program for stimulating scientists-to-scientist communication through support of brief collaborative research projects and support of international workshops on critical research areas is being negotiated with the International Union Against Cancer (UICC) in Geneva. Discussions with the World Health Organization (WHO) in Geneva will lead to the establishment of a center for exchange of cancer information with developing countries.

The National Library of Medicine has a vital concern for the international exchange of biomedical informaiton. The library's mandate to collect and organize health literature published all over the world has resulted in the development of an unparalleled collection of over 1½ million items, in more than 70 languages.

To help meet the needs of health research, education, and practice, the Library lends material from its collection to individuals and institutions all over the world. This year, of the approximately 175,000 loan requests that will be filled at NLM, some 25,000 will go to requesters in other countries. This latter figure includes almost 20,000 loans to 48 developing countries where modern medical information is unavailable because of inadequate library facilities, collection, and staff. These loans are funded under a special arrangement with the U.S. Agency for International Development. NLM also provides reference services, computerized bibliographic searches, and subscriptions to its bibliographies and indexes to these developing countries under the AID arrangement.

In addition to international loan services, the Library also has exchange arrangements with about 900 institutions in 85 countries. These allow the NLM collection to be enriched with considerable material, published in foreign lands, which would be otherwise difficult or impossible to obtain. In return, NLM sends bibliographies and indexes of comparable value that it produces.

The primary international publication of the Library, the monthly Index Medicus, contains references to journal articles in more than 2,300 leading biomedical journals. About half of the 8,000 subscriptions are from foreign institutions, and about 40 percent of the articles indexed are in languages other than English. To help index this material the NLM has formal quid pro quo arrangements with institutions in eight countries. Under these agreements, the foreign centers index journals from their geographic areas and send this input to the National Library of Medicine. The Library, in turn, provides the foreign centers with computer tapes and documentation based on this indexed material so they can provide computerized reference retrieval services in their own and neighboring countries. This computerized service is known as Medlars—medical literature analysis and retrieval system. The cooperating partners are in the United Kingdom, Sweden, France, Germany, Japan, Australia, Canada, and the World Health Organization (Geneva, Switzerland).

In cooperation with the National Cancer Institute, NLM has made its computer system available for cancer-related information (abstracts, citations, descriptive information). These data bases, which form a part of the NCI International Cancer Research Data Bank, are

accessible in the United States and in the eight foreign centers mentioned above, and, through these centers, in other countries which rely on the centers for computerized retrieval services.

SCIENTIST-TO-SCIENTIST COMMUNICATION SYSTEM

Mr. MICHEL. You state that there is no need or desire for fundamental changes in the scientist-to-scientist communication system. Does that mean we can be completely confident that the current information available is being used to the best advantage and that duplication is minimal?

Dr. LAMONT-HAVERS. As I indicated in my opening statement we believe that there is room for improvement, particularly in the application of technology to the processes of storage and retrieval of research-derived information, as well as for the development of new methods to improve the access of scientists to such information. We need, however, to retain the safeguards built into the present systems of communications among scientists to avoid widespread dissemination of unconfirmed or premature announcements and to prevent premature and possibly dangerous use of scientific or clinical reports based on inadequate data. From our many contacts with scientists and our experiences in research activities we believe that fundamental changes in methods of scientist-to-scientist communication are not desirable.

We believe that in almost all instances currently available information is being used to the best advantage by the scientific community. Of course, in the individual circumstances such use depends also upon the motivation and resources of the investigator.

While wasteful duplication of effort is to be avoided much is to be gained through validation of findings by different researchers. The results of a successful experiment must be capable of confirmation in other laboratories. Duplication, as such is not necessarily detrimental. The competent investigator will always begin his work with a careful review of the work of others on the problem he is addressing. Much of our effort to improve scientist-to-scientist communication is directed to facilitating the researchers review of work in his field of interest.

INFORMATION DISSEMINATION

Mr. MICHEL. What offices within HEW are involved in the dissemination of this type of information, as well as the other two types of communication linkage?

Dr. LAMONT-HAVERS. All of the agencies of the Public Health Service engage in communication of research information to scientists, to health practitioners and to the public, with the mix among the target audiences varying according to the agency's principal missions. ADAMHA's activities in this area are quite similar to those of NIH. The same is true of the research components of FDA, HRA, HSA, and CDC. Practicing health professionals and the public are also principal targets of FDA and HRA and various programs of HSA and CDC. The Bureau of Health Education, CDC, is the HEW's focus for coordination of its health education activities for the public.

Mr. MICHEL. How many employees of the Government are involved in the process, and how many dollars are being spent for this purpose?

Dr. LAMONT-HAVERS. The 17 NIH Offices of Scientific and Technical Reports employ 106 persons. In addition, the staffs for special activities like the national high blood pressure education program, the national sickle cell disease program and the control and demonstration programs of the National Heart and Lung Institute and the National Cancer Institute are heavily involved in communication efforts. Also, in any given year a large number of our scientists participate in communication efforts.

Thus, communication activities are integrated into almost every program of the NIH.

The identifiable costs of the Offices of Scientific and Technical Reports are estimated at: $1,590,000 for personnel in fiscal year 1975; $2,580,000 for publication in fiscal year 1975.

The total budget of the National Library of Medicine is also properly attributable to biomedical communications—a total of $28,448,000 in 1975. Four hundred and sixty persons are employed by the Library of Medicine.

OTHER GOVERNMENT AGENCIES INVOLVEMENT

Mr. MICHEL. Are any government agencies, besides HEW, fostering programs in this area, or are we looking at the whole picture?

Dr. LAMONT-HAVERS. The National Science Foundation, the Department of Defense, and the Veterans' Administration all conduct or support biomedical research activities. In the course of such efforts they use publications and other forms of communication for dissemination of research findings among scientists. The Veterans' Administration in particular has close relationships with many academic medical centers and thus is involved in communicating research information to health professionals as well as students in the various health professions.

The Environmental Protection Agency has a "technology transfer" unit which is concerned with communication of scientific information to scientists, professionals and the public.

The National Technical Information Service, operated by the Department of Commerce, is an important communication center for research information derived from Federal support in all fields, including biomedical findings.

The Science Information Exchange of the Smithsonian Institution receives, organizes and disseminates information about research in progress in the life, physical and social sciences.

The Agricultural Extension Service of the Department of Agriculture cooperates in health educational activities in many localities.

The National Institutes of Health and other of the Public Health Service Agencies work cooperatively with the several other Federal agencies involved in the communication of biomedical information.

Mr. MICHEL. Thank you.

ADEQUACY OF NIH BUDGET

Mr. FLOOD. Mr. Conte.

Mr. CONTE. As a health professional, are you satisfied with the budget for the National Institutes?

Dr. LAMONT-HAVERS. As I said in my opening statement, no rational NIH budget will ever suffice to satisfy the demands or meet the opportunities for meritorious biomedical research. However, a lot of important work will be supported with the $1.8 billion requested. It has already been emphasized, by the chairman and other members of the committee, that this amount is some 14 percent less than the appropriations for fiscal year 1975 and this, of course, will present some problems. But I believe—and certainly hope—that these problems are manageable. In view of the administration's overall budgetary policy to cope with the very serious problems of inflation and recession, which also constitute serious threats to the continued support of research, I believe, as I have already said, that it is entirely reasonable that NIH bear its fair share of anti-inflation and anti-recession budgetary measures.

Mr. CONTE. Given the overall amount proposed for the National Institutes, are you personally satisfied with the distribution of funds between individual institutes?

Dr. LAMONT-HAVERS. The distribution of funds is the result of a number of factors. As I said in my opening statement, it is the resultant of societal pressures, the policies of the Federal Government, and the scientific opportunities for productive research. There is much room for differences of opinion here. My personal view is that, relatively speaking, we are putting a little too much emphasis on cancer research and not quite enough on our efforts to gain a really thorough understanding of basic biological processes. Research on molecular biology may well solve more medical problems than frontal attacks on specific diseases. However, some of the cancer funds do support research in molecular biology which will, predictably, shed light on many problems outside the immediate field of cancer. I am, therefore, not unhappy with the present distribution of effort though my personal decisions might have been somewhat different.

Mr. CONTE. Again, taking that total amount as given, are there any Institutes which you feel might have received higher or lower priority?

Dr. LAMONT-HAVERS. The areas covered by all the Institutes are important to the Nation's health and it is difficult to choose between them, but it would, for example, be desirable to give a somewhat greater push to research on environmental health problems.

I certainly do not think that the budget request for any Institute is too high in relation to the needs of its mission and so there is none to which I would give a lower priority. As you know, one-third of the total amount requested for all Institutes is for the Cancer Institute. I would be inclined to give all the other Institutes a somewhat higher relative priority. But that does not mean that the cancer funds will not be well spent.

MORALE AT NIH

Mr. CONTE. There have been recent newspapers articles about low morale at NIH, about good people leaving, and so forth. Would you care to comment on the morale situation at NIH, and what might be done to help that situation?

Dr. LAMONT-HAVERS. I suspect that the stories about low morale at NIH are somewhat exaggerated but there have been several events that many people on our staff have found disturbing.

The most important of these, by far, has been the personnel squeeze which has forced us to close one or two laboratories and has, as I have already said, sharply reduced the number of supporting personnel and hence the services available to our in-house scientists. We have done what we can to mitigate the situation and it is, at the moment, relatively manageable. However, I believe that further erosion of personnel, especially in the intramural area, would indeed have a bad effect not merely on morale but on the effectiveness of the work being done.

The second factor, which affects our senior scientists and administrators, is the ceiling on salaries. For highly qualified and really competent people in the senior grades, the civil service scale compares unfavorably with salaries paid by leading academic institutions and other nongovernmental research organizations to men and women of comparable talent and responsibility. There is not much we can do about this except to make NIH, in comparison, a more attractive place to work than the competing post with the higher salary. In the past, this has, indeed, been the case but it is becoming more difficult to maintain this differential with the contraction of supporting services and the difficulties of modernizing some of our aging research facilities.

There are other matters that have tended to ruffle feathers among NIH personnel such as the rather abrupt dismissal of two Directors of NIH and the sometimes strained relationships between some of our extramural people and some of those in the Office of the Assistant Secretary for Health. But this situation is, I believe, improving and with a little show of good will on both sides—which I am sure exists—will not be a significant factor in the future.

In discussing morale at NIH during the past year or so it would be dishonest not to mention the effect of the atmosphere, within the executive branch, during what I suppose one would call the Watergate days. That episode is now, however, behind us and its affect on morale—which was very real at the time—has been dissipated.

On the whole, then, I would say that we have some personnel problems but that morale, as such, is really very good. The people at NIH believe strongly in the mission of NIH; with very few exceptions, they are dedicated to their work and get along well with each other; they are proud of NIH and proud to be part of NIH. I believe that NIH is still a happy ship.

COMPARISON WITH FISCAL YEAR 1975 APPROPRIATIONS

Mr. CONTE. Just so we have it in the record, would you provide a listing of the proposed budget for each Institute, the change and percentage change from the 1975 appropriation, and the number of positions gained or lost from 1975?

Dr. LAMONT-HAVERS. I shall be glad to.

[The information requested follows:]

Insert to 3143

1976 BUDGET REQUEST OVER 1975 APPROPRIATION 1/
(In thousands of dollars)

	1975 Appropriation		1976 Request		Change over 1975 Appropriation		
	Pos.	Amount	Pos.	Amount	Pos.	Amount	%--$'s
Research Institutes & Div.:							
Cancer	1,906	$691,361	1,836	$605,000	-70	-$86,361	-12.5%
Heart	711	323,884	691	292,794	-20	-31,090	-9.6
Dental	272	49,833	268	43,536	-4	-6,297	-12.4
Arthritis	566	172,980	556	148,409	-10	-24,571	-14.2
Neurology	513	142,034	510	114,955	-3	-27,079	-19.1
Allergy	593	119,369	587	108,711	-6	-10,658	-8.9
General medical sciences	155	187,290	152	161,630	-3	-25,660	-13.7
Child health	358	126,067	349	106,062	-9	-20,005	-15.9
Aging	175	15,722	173	16,190	-2	+468	+3.0
Eye	142	44,040	132	39,201	-10	-4,839	-11.0
Environmental health	240	34,937	238	31,113	-2	-3,824	-10.9
Research resources	75	128,250	72	81,058	-3	-47,192	-36.8
Fogarty center	51	5,406	49	4,540	-2	-866	-15.4
Total Research	5,757	2,041,173	5,613	1,753,199	-144	-287,974	-14.1
Nat'l Library of Medicine	475	28,448	468	28,815	-7	+367	+1.3
Buildings and Facilities	.....	3,000	.....	3,000	.....	.....	.....
Office of the Director	549	17,986 2/	546	19,986	-3	+2,000	+11.1
(Management fund)	3,301	(87,406)	3,316	(91,621)	+15	(+4,215)	(+4.8)
(Service and supply fund)	626	(44,398)	614	(47,382)	-12	(+2,984)	(+6.7)
TOTAL NIH	10,708	2,090,607	10,557	1,805,000	-151	-285,607	-13.7

1/ Comparable

2/ Includes proposed supplemental

RELATION TO HEALTH CARE SYSTEM

Mr. CONTE. Last year we were told that outside of the cancer and heart programs, there were no specific program efforts directed at introducing biomedical research results into the health care system. Is the situation still the same, or have you made some progress in this area? What actions are you taking to disseminate research findings from all of the Institutes into the health care delivery system?

Dr. LAMONT-HAVERS. The situation is essentially the same because none of the other Institutes has legislative authority to engage in demonstration and control programs. However, we are much concerned about making immediately usable research result more readily known to and available to practitioners. Our plans are spelled out in a report which we have just, today, submitted to the committee. I think you will find that we will, in the future, be making a much more concerted effort than we have in the past.

LEADING CAUSES OF DEATH

Mr. CONTE. Would you provide the 10 or 12 most serious diseases in the United States along with the number of fatalities from that disease each year for the past couple of years, and the Institutes which are directly or indirectly involved in research on that disease? And also, if you would, please include the amount of money being spent on Federal research into each disease.

Dr. LAMONT-HAVERS. I shall be glad to supply this for the record. However, we may have some difficulty in showing how much is spent by all Federal agencies for research on specific diseases. We can supply such figures for NIH but I am not sure whether we can do it for all agencies. We shall do our best.

[The information requested follows:]

Insert to 3143 5

Ten Leading Causes of Death in FY 1973 and NIH Funding for FY 1975[1]
(Dollars in millions)

Cause	Deaths per 100,000 pop.	% of all deaths	1975 Col. of 1976 Pres. Bud.[1]
All causes	942.1	100.0	-
Diseases of heart	359.5	38.2	$119.2
Malignant neoplasms, all forms	168.4	27.9	691.4
Cerebrovascular diseases	102.3	10.9	21.1[2]
Accidents	54.8	5.8	5.2[3]
Influenza and pneumonia	29.1	3.1	9.1[4]
Diabetes mellitus	17.4	1.8	13.3
Cirrhosis of liver	16.0	1.7	-[5]
Arteriosclerosis	15.9	1.7	64.9
Certain causes of death in early infancy	14.8	1.6	-[6]
Bronchitis, emphysema and asthma	14.4	1.5	49.4[7]
Other	149.4	15.9	-

[1] Includes only funds specifically budgeted, though applicable undifferentiated activities may be supported. All NIH funding mechanisms (e.g., training support) are shown if directly applicable.

[2] NHLI budgeted item + stroke (NINCDS).

[3] Trauma and burn research centers.

[4] Influenza and other viral respiratory infections.

[5] Not separately budgeted, but is included in research on digestive diseases.

[6] Not separately budgeted, but much of the research supported by NICHD is relevant. Sudden Infant Death Syndrome is not included in this category of diseases.

[7] Lung diseases + asthma and allergic disease centers.

PRIORITIES IN NIH RESEARCH

Mr. CONTE. I wonder if you would talk about the priorities of NIH. It is obvious that cancer is one of them, but could you state your top five or six priorities in NIH research?

Dr. LAMONT-HAVERS. Research on cancer and on heart disease are, of course, our two top priorities as these are the subjects of two national programs. Next would be the areas for which there are new congressional mandates namely, aging, diabetes, and arthritis. Then I would add research on environmental health for which there is a societal demand and certainly an urgent societal need. However, apart from these specific programs, we give a high priority to research aimed at a real understanding of biological systems such as, for example, research on genetics and the cellular and molecular basis of disease which I believe will, in the long run, make the most dramatic contributions to the conquest or amelioration of disease.

CANCER RESEARCH

Mr. CONTE. In cancer research, aren't you essentially waiting for the breakthrough?

Dr. LAMONT-HAVERS. No, sir. In medical research, as in all scientific research, knowledge provides the power to solve problems. Waiting for a breakthrough is like trying to accumulate an estate by waiting for an inheritance from a rich relative about whose existence you are not sure. You may be lucky but you'd be surer of success if you did a little systematic saving. Success in science is based on the systematic buildup of knowledge—a step at a time. That is how cancer research is also proceeding.

Mr. CONTE. Isn't it possible that a major advance in cancer could come out of one of the other Institutes, Arthritis or General Medical Science, for example?

Dr. LAMONT-HAVERS. Yes—it is not only possible, I am tempted to say that it is probable. Biomedical research is much more intertwined than the rather arbitrary organization of NIH into disease-oriented Institutes would imply. There have been many instances in the past of the answer to some problem—or a crucial part of such answer—being found through research supported by what one might say was the "wrong" Institute.

In a very real sense, the human body is one mechanism—not just a collection of separate organs. By the same token, biomedical research is indivisible. Any one investigator may be working on only a very small area but his findings may—and very often do—have relevance in many other areas.

Mr. CONTE. Can you justify the tremendous emphasis on a specific Institute?

Dr. LAMONT-HAVERS. In terms of societal concerns or national policy one can—and we obviously do. The Congress decided, through legislation, that special emphasis be given to research on cancer and on heart and lung diseases. On purely scientific grounds, I doubt that the same conclusions would have been reached.

Mr. CONTE. What progress has been made in cancer over the past year? How about in heart disease?

Dr. LAMONT-HAVERS. If I may, Mr. Conte, I should like to leave this question for Dr. Rauscher who will testify in detail this afternoon on progress in cancer research and for Dr. Ringler who will testify tomorrow about progress on heart disease.

GRANT APPEALS PROCEDURE

Mr. CONTE. Last year we were told that there had been some discussion of an appeal procedure for the review of research and training grant applications. Has there been any more discussion of this, and is anything along these lines underway?

Dr. LAMONT-HAVERS. NIH has implemented the departmental policy in this matter and has published the appeal procedure for disputes arising after an award has been made. This procedure is entirely about administrative and management problems. There is no mechanism for appealing the scientific judgment of the peer review panels on the scientific merits of grant applications. Appeals concerning that kind of judgment would completely undermine and negate the peer review system which has served admirably to maintain the high standards of NIH programs. Indeed, the Congress last year, in the Cancer Act, instructed the Secretary to publish Federal regulations formalizing the peer review system as presently constituted.

REDUCTION IN POSITIONS

Mr. CONTE. Over the past several years, hasn't there been a reduction of positions outside of the Cancer and Heart Institutes? Do you feel that the other Institues have sufficient positions to properly carry out their functions?

Dr. LAMONT-HAVERS. I think I am right in saying that none of the Institute and Division Directors regards the positions available as sufficient. Most of the Institutes now have less staff than they had in 1968. The exceptions are Cancer and Heart and the two newest Institutes: Eye and Environmental Health. However, all of the Institutes will have fewer budgeted positions in 1976 than they had in 1975. I shall be glad to supply for the record, a table comparing the budgeted positions in 1968, in 1975, and proposed for 1976.

[The requested information follows:]

BUDGETED POSITIONS IN 1968/1975 AND REQUESTED FOR 1976

	Fiscal year—				Fiscal year—		
	1968 budgeted positions	1975 budgeted positions	1976 budgeted positions		1968 budgeted positions	1975 budgeted positions	1976 budgeted positions
NCI	1,419	1,906	1,836	DRR	84	75	72
NHLI	682	711	691	FIC	51	51	49
NIDR	321	272	268	NLM	536	475	468
NIAMDD	697	566	556	DCRT	379	256	256
NINCDS	732	513	510	DRS	693	530	530
NIAID	746	593	587	OA	1,796	1,664	1,664
NIGMS	215	155	152	PD	144	135	150
NICHD	478	358	349	CC	1,622	1,500	1,500
NIA		175	173	DRG	569	391	376
NEI	61	142	132				
NIEHS	171	240	238	Total	11,396	[1] 10,708	10,557

[1] Employment ceiling for fiscal year 1975 is 10,452.

NAS STUDY ON MANPOWER NEEDS

Mr. CONTE. Last year we were told that a survey of the National Academy of Sciences showing the results of past training in NIH fellowship programs would be ready this year. Is it finished? If it is, could you tell us some of its conclusions?

Dr. LAMONT-HAVERS. It is not yet finished, Mr. Conte. In fact, the actual study is only just beginning. Before agreeing to undertake the study the NAS did a feasibility study which has only just been completed. The conclusion of that preliminary study is that, despite some difficulties, the full study, requested by the Congress, is feasible and will be undertaken.

UNFUNDED GRANT APPLICATIONS

Mr. CONTE. How many approved and unfunded grant requests did you have in 1974? How many of those were first-time applicants? Would you compare those figures with those for the previous year?

Dr. LAMONT-HAVERS. I shall be glad to supply this for the record.

[The information follows:]

Number of competing NIH research grant applications approved by the Advisory Councils but not funded were:

	Total	New	Renewal
Fiscal year:			
1973	3,432	2,567	865
1974	3,573	2,713	860

Our records of chief investigators, as shown on grant applications, going back to fiscal year 1968 indicate that of the 2,567 new applications, which were approved but not funded in fiscal year 1973, 969—or 38 percent—were from first-time applicants. In fiscal year 1974 there were 942—or 35 percent—first-time applicants out of 2,713 new applications.

GENERAL RESEARCH SUPPORT GRANTS

Mr. CONTE. How much money are you putting into general research grants this year? How many grants will you award?

Dr. LAMONT-HAVERS. The fiscal year 1975 appropriations for general research support grants is just short of $43 million. However, the program is being discontinued and there are no funds for it in the fiscal year 1976 budget request. This year we will make 340 such grants.

RESEARCH CONTRACTS

Mr. CONTE. What percent of your budget goes for research contracts? How many research contracts do you presently have in effect? How many project officers do you have to administer those contracts?

Dr. LAMONT-HAVERS. For fiscal year 1974, for which our records are complete, NIH obligations for contracts were 15 percent of the total NIH budget. This does not mean that this is uniform across the institutes. NCI spends a considerably higher percentage of its budget on contracts, while other B/I/D's spend a very small amount.

We made 1,910 research and development contract awards in fiscal year 1974. The number of project officers assigned to contracts in that

year was 496. This does not mean that there were four projects per project officer. There is a range from 1 contract per project officer to a much larger number, as high as 20. In the latter cases, assistant project officers, who are not identified in our information system, may be used.

Mr. CONTE. Are these project officers sufficient to properly keep control over the contracted work?

Dr. LAMONT-HAVERS. The workload per project officer varies considerably from institute to institute and from program to program within institutes. This is because we have some personnel constraints and because different types of contracts require different degrees of monitoring. For example, a contract involving clinical research requires more attention on the part of a project officer than a laboratory research project where the investigator is given a certain degree of freedom in the prosecution of work toward a defined goal. In the former case, the questions of appropriate informed consent and of the other issues involved in clinical research require care on the part of the investigator and the project officer. In the latter case, the measurement of performance cannot really be done on a short-term basis; so the assessment of the project's success is done by examination of periodic and final project reports, and otherwise the project officer is involved only in occasional problems of scientific administration of the contract.

Mr. CONTE. Do you see any sort of trend in the use of research contracts? Would you speak to the rationale for contractual research as opposed to grant research?

Dr. LAMONT-HAVERS. There has been a trend toward the use of contracts for a great deal of applied research, such as the testing of carcinogens and of drugs, against cancer and epilepsy for example. NIH also uses contracts for clinical research when a controlled trial involving many institutions requires supervision and coordination. Vaccine-development and testing is also done on a contractual basis. Also, various other programs for development of cardiac assist devices, and of instrumentation for biomedical research or medical care, are appropriaitely done by contract. When fundamental research has produced knowledge on which to base a targeted program to achieve a particular goal, the contract is appropriate. Since, in recent years, there has been accrual of knowledg because of past generous support of grants, there have developed a number of programs which can "take off" from that knowledge base.

NIH has developed a set of guidelines for the appropriate use of the grant and the contract. The grant is used for the support of investigator-initiated research, where the grantee defines the problem, the approach, et cetera. The grantee is given freedom to pursue his own leads, without any surveillance. The contract is used where NIH defines the questions and establishes the goals.

There have been some programs in which the contract has been used to support basic research, as in the cancer virus program, about which there was criticism by the Zinder committee, as you may know. NCI has recently announced a new program, the cancer research emphasis grants (CREG), which are intended to replace contracts in the area of fundamental virological research related to cancer, and other areas as well.

REVIEW OF CONTRACTS

Mr. CONTE. What sort of a review procedure do you use for the awarding of contracts?

Dr. LAMONT-HAVERS. We have used a variety of procedures, all designed to mimic the peer review procedures for grants. Proposals received in response to a solicitation of offers to do a particular project (an RFP) are examined by a group of experts and evaluated against a set of evaluation criteria which are published in the RFP. This is the initial technical merit review, and in most Institutes it is done by outside consultants. On occasion, an Institute has asked a particular study section to perform such a review, but more often the consultant panel is established by the Institute itself. The panel may be drawn from the program advisory committee chartered to provide to the Institute scientific advice and recommendations as to research or development goals, or it may be made up of outside scientists assembled solely for the purpose of examining the proposals for one or a few separate projects.

A second review of the proposals judged most meritorious is done at the level of the Director of an Institute, or in the case of those Institutes with bureau status, at the Division Director level. Immediate scientific and administrative staff participate. This review is done to assure program balance in relation to available funds, and to assure the Director that an appropriate evaluation has been accomplished.

In the case of research or development contract projects for which NIH components specify precisely what they want done and little or no leeway is given to the contractor as to his approach to the project, it is inappropriate to waste the time of outside experts merely to judge the capabilities and facilities of offerors submitting proposals. It is more appropriate to have advice at an earlier stage, at the time of the decision as to whether or not the project should be done in the first place. We expect that the Institutes and Divisions of NIH will document the deliberations on that issue in the minutes of advisory groups. This is consitent with the conference report on the National Cancer Act amendments of 1974 (Public Law 93–352), which gives a very cogent explanation of the language of the act on this point. The act states, in section 472, "the Secretary * * * shall by regulation require appropriate scientific peer review of:

"(1) application * * * for grants * * * for biomedical and behavioral research; and

"(2) biomedical and behavorial research and development contract project. * * *" "Projects" is the word to emphasize.

It then stipulates that peer review groups will be composed of no more than 25 percent Federal officials with the rest to be outside experts. We are preparing the final draft of the regulations on this point at the present time.

Mr. CONTE. I have heard that you have an excellent review procedure for grants, but that your system for contracts is somewhat inferior. Would you care to comment on that?

Dr. LAMONT-HAVERS. I believe that the impressions that some scientists have about contracts is due to a lack of understanding of our procedures for initiating projects and reviewing proposals. While the grants system operates in a manner which most non-Federal scientists have become accustomed to, the contracts operations are not so clear.

For example, any scientist can look in our publication "NIH Public Advisory Groups" and identify the members of the study section which will review his or her grant application, and, also, the information is available as to when the review will take place and to what Institute the application has been referred. On the other hand, contract proposals are solicited and received for individual pieces of work and, even in cases where there is an established program committee, the review may be conducted by only a part of the committee membership, selected for their expertise as it relates to the particular project. It is much more difficult to provide the membership of the review group to the general scientific public in each case. Moreover, as I have pointed out in answer to one of your earlier questions, contracts are frequently awarded for rigid protocol studies, development, and applied research, and some scientists disdain the projects as being too far back from "the leading edge of science." On these bases, their perceptions of NIH contractual activities are that they are second class as compared with grants. However, the work being done is necessary, and the results in the development of drugs, vaccines, devices, and instruments have been profitable. I believe that as more and more of our scientists learn about our contractual activities and of our attempts to achieve equity in the review of proposals, their impressions concerning the inferiority of contracts will diminish. We are doing better about communicating information on our contract operations by use of a publication called NIH Guide for Grants and Contracts. I will be glad to send you a copy of this if you wish.

LOCUS OF RESEARCH CONTRACTS

Mr. CONTE. Again, with regard to research contracts, what percentage go to commercial researchers and what percentage to academic researchers?

Dr. LAMONT-HAVERS. Again, I must use fiscal year 1974 figures; 15.2 percent of our contracts were awarded to commercial organizations, 49.8 percent to academic institutions, and 35 percent to nonprofit research institutes and hospitals. As to percentage of research contract dollars, 28.6 percent went to commercial organizations, 41.9 percent to academic institutions, and 29.5 percent to nonprofits.

CROWDED CORRIDORS OF CLINICAL CENTER

Mr. CONTE. One final question. One of my staff members used to work at NIH. He told me that in the Clinical Center there are stacks and stacks of materials in every corridor, many of which have to be thrown away because they are kept beyond their date of acceptable potency; that's with supplies of chemical reagents and biologicals. I have heard that there is just more money being pumped into that place than can be effectively used, and that a lot of it is being wasted. Would you respond to that? Can you really use all the money being appropriated for NIH?

Dr. LAMONT-HAVERS. Well, there is no doubt that the corridors of the Clinical Center are crowded with equipment—that is, the corridors on the north side of the building which is entirely given over to laboratories. In fact, this is true of the corridors in virtually all of our laboratory buildings. It is a symptom of our acute shortage of space.

The expansion of the cancer and heart programs and the creation of new Institutes—for child health and for eye research—has, of course, increased the need for laboratory space and has, inevitably, resulted in crowding. We have plans, as you know, for a building for the Child Health Institute but its construction seems, as yet, to be some time in the future. Meanwhile, we are accommodating their intramural program as best we can.

Most of the stuff in the corridors is either equipment that is used intermittently, or that is not needed for the time being, or consumable supplies for which there is no room inside the laboratory modules. We periodically inspect the situation and launch a campaign to get the corridors cleared up a little—at least enough not to impede traffic. The resulting improvement is quite temporary, however, as there really is no good solution for much of the problem under present space limitations.

I doubt that there is much wastage of perishable supplies but I shall certainly look into that aspect of the situation.

To some extent, messy corridors are a traditional and apparently inevitable concomitant of busy laboratories. Dr. Stetten—who, as Deputy Director for Science, is the boss of our intramural program—wrote an article on this subject a few years ago when he was dean of the Rutgers Medical School. Its title is "Notes on the Competition for (Inner) Space." It is relevant to your question and, as it is both amusing and informative, I should therefore like to submit it for the record.

[The article referred to follows:]

NOTES ON THE COMPETITION FOR (INNER) SPACE

*DeWITT STETTEN, JR.**

The commodity prized above all others by the laboratory scientist is space. To gain an increased assignment of laboratory space, many a scientist will lie to his superior, knife his co-equal, or fire his junior. An occasional scientist has lent his spectrophotometer, has shared his latest experimental results, has given away a sizeable portion of his income, but rare indeed is the scientist who has graciously permitted invasion of his domain of laboratory modules. Money, shirt, or wife he may give away, but yield one square foot of laboratory space? Never! Even in retirement the typical scientist will exert all possible pressures, pull all possible wires, to retain dominance over the laboratory area which had been assigned to him in his heyday.

If space is indeed so precious a commodity to the working scientist, it may merit our brief attention. Space is the recognized medium of currency over which the dean bargains with his professors, the department chairman with his staff. The power wielded by the administrative officer depends upon his power to distribute space, together with other perquisites, among the working scientists. There is a deeply rooted but totally erroneous rumor that the research accomplishment of a laboratory worker is somehow related to the area of laboratory space which he controls. A massive assignment of space is of course a cherished status symbol, as revealed by the fact that when one visits a fellow scientist he will often exhibit his rooms before presenting his colleagues or revealing his research activities.

It is surely not surprising that space should have come to assume so important a place in the thinking of the scientist. The common law divides man's possessions into his *real* estate—i.e., land and fixed improvements—and his *personal* estate, which is everything else. This distinction imparts to all property other than land an unreal character. Of the many ele-

* Dean, Rutgers Medical School, New Brunswick, New Jersey.

ments entering into a research program, clearly the insubstantial ones—the idea, the ingenuity, the wisdom, and the drive—are of greatest importance. These do not, however, lend themselves to ready accounting. The more substantial elements include dollars, staff, equipment, materials, and space, and of all of these the one likely to be least elastic, hence most *real*, is space. With persistence and ingenuity, more dollars can usually be found, and given more dollars, more equipment and materials can be purchased, more staff may be retained. But regardless of available money, additional space is generally not for sale. Space is a hard architectural fact, ultimately limited, in many instances, by virtually immutable judgments made many years before. Laboratories will overflow into offices, into corridors, but soon a limit is reached and it is this, the limiting nature of available space, which exaggerates its importance. It is the inelastic nature of space which makes it the *real* element in a program of scientific research.

When a scientist is awarded his Ph.D. or other higher degree he is told by the president of his university that he may now enjoy "the rights and privileges pertaining thereunto." Usually there is no clarification of precisely what these privileges may be, and it devolves upon the present writer to reveal one of them. This is the inalienable right to complain of overcrowding. It should particularly be noted that this right is inalienable, by which is meant that the right to complain obtains whether or not overcrowding exists. Correction of overcrowding in no wise eliminates the right to complain, and, indeed, experience has shown that the administrator who aims to silence such complaints by the award of more space will inevitably be disappointed. The creative mind must rebel against the restraints of its environment. The less elastic the restraint, the more irritating it will be; and, as pointed out, space is the least elastic of environmental factors, hence the most likely to irritate. This leads to our first conclusion.

RULE I. THE RESPONSIBLE SCIENTIST HAS THE INALIENABLE RIGHT TO COMPLAIN OF OVERCROWDING, AND NOTHING SHALL BE DONE TO ABROGATE THIS RIGHT.

But is there truly overcrowding? The answer to this question requires a subjective judgment in the isolated case. As one wanders from one academic laboratory to another, one is, I believe, ultimately forced to conclude that, yes, in many laboratories there is indeed overcrowding. It is, however, not uniformly distributed, and the distribution of overcrowding

appears to correlate positively, as might be anticipated, with the general scientific excellence and productivity of the institution. The foot-loose population of postdoctoral fellows, being made up of shrewd judges of scientific excellence, will tend to congregate in the most active scientific centers and will in turn contribute to the scientific activity. When a laboratory is truly lightly occupied, underpopulated, one of two conditions will usually be discovered. Either there has been substantial construction completed so recently as to preclude occupancy by scientists, or that laboratory suffers from some loathsome disease. This disease may be a wage scale below competitive standards, a misguided administration, an excessive teaching burden, an infringement of academic freedom, or any of the other conditions repulsive to scientists. A well run and healthy research institute may expect to be overcowded within six to twelve months after completion of its latest building program, which leads to our second conclusion.

RULE 2. THE DEGREE OF CROWDING IN A LABORATORY IS ALMOST ALWAYS POSITIVELY CORRELATED WITH THE SCIENTIFIC EXCELLENCE AND ADMINISTRATIVE HEALTH OF THE INSTITUTION.

The wise administrator grasps fully the import of this rule. As he strolls through his institution, he is overjoyed when he sees a crowded laboratory, dismayed when he finds an underpopulated one. He will, however, be well advised to conceal these emotions. Nothing appears to disturb a scientist quite so much as to be congratulated when he approaches his superior to complain about local overcrowding. Hypocritical sympathy would appear to be the more diplomatic attitude to assume.

But of what does overcrowding consist? We all know that some of our friends are most comfortable when sharing an 8′ × 10′ laboratory module with five colleagues while others are distressingly overcrowded when deposited alone in a room of 600 square feet. All that this means is that each individual has a "threshold of overcrowding," a maximum density of colleague population which he can comfortably tolerate. Let the density of population increase ever so slightly above this threshold and our man becomes acutely uncomfortable. The actual threshold, measured in people per square feet, will vary widely from man to man but appears to be reasonably constant for a given scientist. Which brings us to our next conclusion.

RULE 3. EACH SCIENTIST HAS HIS OWN THRESHOLD OF OVERCROWDING BELOW WHICH HE FUNCTIONS COMFORTABLY AND ABOVE WHICH HE IS UNCOMFORTABLE.

The reader is reminded that, by Rule 1, whether our scientist is in an environment below or above his threshold, whether he is comfortable or uncomfortable, he still has every right to complain and often will do so. The scientist-administrator, department chairman, or dean generally has a small bonus added to his salary to reimburse him for the pain and tedium associated with the obligate listening to such complaints. And this brings us to the last question, which is: How should the administrator respond to the complaint of overcrowding? If he is young and inexperienced or, indeed, if he is old and tired, the administrator may yield to the persistently complaining scientist and by new construction or other magic may award him additional space. If the scientist is a truly creative person, this may be a good thing to do. But if it is done in the hope of silencing the complaint, it will have been done in vain.

Assuming our scientist to be an excellent one, he will already have attracted postdoctoral fellows and will have raised funds to retain professional associates and technical support. He will have populated the laboratory space assigned to him to a density equal to or greater than his own threshold by the time the administrator heeds his complaints. If more space is assigned to such a man, he will within a short while attract additional staff into his program, and once again a population density equal to his threshold will supervene. Not only will the complaining continue but, indeed, the basis for the complaint will again be there. Our final conclusion follows.

RULE 4. THE AWARDING OF ADDITIONAL SPACE TO THE SCIENTIST WHO IS OVERCROWDED AND COMPLAINS THEREOF WILL NEITHER PERMANENTLY RELIEVE THE OVERCROWDING NOR QUIET THE COMPLAINT.

The wise and vigorous scientist-administrator may discover, in these four rules, some guide lines to assist him in his judgments about laboratory space assignment. If he fails to detect such guiding principles, he can always fall back upon such rules of thumb as promulgated by one of our great institutions: 200 square feet net per warm body unless the body be that of a graduate student. For reasons which elude the present writer, graduate students are to be compressed, by this rule of thumb, into 100 square feet each. The means for securing such compression have not yet been revealed.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. FRANK J. RAUSCHER, JR., DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE NATIONAL INSTITUTES OF HEALTH
DR. BAYARD H. MORRISON III, ASSISTANT DIRECTOR, NATIONAL CANCER INSTITUTE
CALVIN B. BALDWIN, JR., EXECUTIVE OFFICER, NATIONAL CANCER INSTITUTE
EARLE L. BROWNING, FINANCIAL MANAGER, NATIONAL CANCER INSTITUTE
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, COMPTROLLER FOR BUDGET

Mr. FLOOD. The committee will come to order.

This afternoon we will take up the National Cancer Institute of the National Institutes of Health.

The presentation will be made by Dr. Frank J. Rauscher, Jr., the Director.

We know Dr. Rauscher well in the committee and have a very high regard for him.

We will insert your biographical sketch, Dr. Rauscher.

[The information follows:]

BIOGRAPHICAL SKETCH OF FRANK J. RAUSCHER, JR., PH. D.

Position: Director, National Cancer Program, National Cancer Institute.

Birthplace and date: Hellertown, Pa., May 24, 1931.

Education: Moravian College, Bethlehem, Pa., 1953, B.S., premedical curriculum; Ph. D., Rutgers, The State University, New Brunswick, N.J., June 1957.

Experience: Present: Director, National Cancer Program, National Cancer Institute; 1970–72 Scientific Director for Etiology, NCI; 1969–70 Acting Scientific Director for Etiology, NCI; 1967–70 Associate Scientific Director for Viral Oncology, Etiology, NCI; 1966–67 Chief, Viral Leukemia and Lymphoma Branch, Etiology, NCI; 1965–66 Acting Chief, Viral Leukemia and Lymphoma Branch, Etiology, NCI; 1964–70 Chairman, Special Virus (Leukemia) Cancer Program, Etiology, NCI; 1964–66 Head, Viral Oncology Section, Laboratory of Viral Oncology, NCI; 1962–67 Visiting Investigator of Viral Oncology, Rutgers University; 1959–64 Microbiologist, National Cancer Institute, Laboratory of Viral Oncology; 1959 Visiting Instructor of Animal Virology, Trinity College, Washington, D.C.; 1958–59 Assistant Professor of Virology, Rutgers University Graduate School, New Brunswick, N.J.; 1957–58 Research Associate in Virology, Rutgers University Graduate School, New Brunswick, N.J.; 1955–57 Research Assistant in Virology, Rutgers University Graduate School, New Brunswick, N.J.; and 1953–55 Research Fellow in Virology, Rutgers University Graduate School, New Brunswick, N.J.

Association memberships: The Theobald Smith Society, New Jersey, Society of Sigma Xi, the American Association for Cancer Research, the American Association of Immunologists, the American Association for Advancement of Science, World Society for Leukemia and Related Diseases, American Society of Clinical Oncology, Honorary Member of American Academy of Microbiology.

Special awards citations, or publications: Comenius Award—Presented annually by Moravian College, Bethlehem, Pa., to a person "for outstanding scientific achievement." April 1963; U.S. Junior Chamber of Commerce Award—Presented to the Nation's "Ten Outstanding Young Men," January 1965; Selman A. Waksman Honorary Lectureship Award—Presented annually by the Theobald Smith Society, the New Jersey Branch of the American Society for Microbiology for "Outstanding Contributions to Microbiology." March 1967; Arthur S. Flemming Award—Presented annually to the "Ten Outstanding Young Men in the Federal Government." February 1968; Vice President, World Society for Comparative Leukemia Research, 1967–72; elected to board of directors, American Association for Cancer Research, 1970; elected—board of trustees, April 1970, of Moravian College, Bethlehem, Pa., for the period 1971–74; appointment—International Agency for Research on Cancer; Member of Scientific Council, 1972–74; Chairman, U.S. Delegation, Governing Council, 1972; Superior Service Award—Presented by the Department of Health, Education, and Welfare. July 1972; Lucy Wortham James Laboratory Research Award—Presented annually by the James Ewing Society, 1973; Honorary Degree of Doctor of Science, Rutgers University, May 31, 1973; and 59 publications on virology, cancer research, cancer planning and biomedical management.

Mr. FLOOD. We would like to meet the people you have with you.

Dr. RAUSCHER. Thank you, Mr. Chairman.

This is Mr. Calvin Balwin, Jr., our executive officer; Dr. Bayard H. Morrison, assistant director; and Mr. Earle Browning, our financial manager.

Mr. FLOOD. How do you want to handle the prepared statement, Dr. Rauscher?

Dr. RAUSCHER. I would like to read it.

OPENING STATEMENT

Mr. Chairman, and members of the committee: Our ability to advance the national effort against cancer was strengthened by the new and expanded authorities of the National Cancer Act Amendments of 1974. We were thus able to accelerate the momentum we have been building in the national cancer program since early 1972.

The goal, simply stated, is to reduce the impact of cancer on people. We aim to develop the means to prevent cancer, to cure it when it cannot be prevented, and to treat it for long-term survival with a good quality of life when it cannot be cured. Every treatment plan will include rehabilitation to restore the patient to productive living.

Mr. Chairman, we have achieved a number of new research results that have advanced our understanding of cancer and our ability to reduce its impact. We can report also that as our cancer control program has become fully operational, we are beginning to see results from extensive activities to promote the widespread application of cancer knowledge in medical and health practice. Much of the progress in research and control already has had a direct impact on people or has a clear potential for benefit to them.

One of the steps we have taken to develop a coordinated national program has been to organize an interagency coordinating committee. Its main purpose is to exchange information on Federal efforts in cancer research and control to avoid overlap and duplication. Fourteen Federal agencies are represented on the committee.

We shall strengthen the network of coordinated research and control programs, as well as coordination in information exchange, manage-

ment, and planning. By this means we hope to achieve the active participation of government at all levels and all components of the private sector.

The proposed budget for fiscal year 1976 is before you. The accompanying budget justifications set forth the major accomplishments under the national cancer program during fiscal year 1975, and the followup and new activities planned for 1976. At this time, I shall present some of the progress highlights.

ADVANCES AGAINST THE MAJOR CANCERS

We believe that the totality of the research and control accomplishments of the past year is significant enough to influence the long-term survival statistics for the three cancers that are responsible for almost 45 percent of deaths due to cancer. These are cancers of the lung, breast, and colon.

In breast cancer, the first results from the nationwide breast cancer detection demonstration we are sponsoring jointly with the American Cancer Society have shown a 28-percent increase in the percentage of women diagnosed with cancer of the breast but no cancer spread to the lymph nodes in the armpit.

The improved diagnoses are due to the use of the techniques of mammography and Xeroradiography to detect breast cancer in symptom-free women. Thus, this program, which is screening annually 270,000 women in 27 projects, is detecting breast cancer at earlier stages than is usual. This will increase the chance for longer survival for the patients because there is a high 5-year survival rate if the disease is detected when the lymph nodes are free of cancer.

BREAST CANCER

Mr. FLOOD. This may sound like a strange question, but is there such a thing as breast cancer in men as distinguished from breast cancer in women?

Dr. RAUSCHER. There is breast cancer in men. It is very rare but very virulent.

Mr. FLOOD. Is it the same cancer?

Dr. RAUSCHER. It is an adenocarcinoma normally.

In treatment of breast cancer, early results of a test of less radical surgery, with or without postoperative radiotherapy, suggest that it may be as effective as radical surgery. If this trend continues, these results should lead to a significant departure from the traditional radical, and in some cases disfiguring, surgery.

Encouraging results were obtained in treatment aimed at preventing recurrence of breast cancer by early introduction of drug therapy after initial surgery. This treatment was a logical step in the development of systemic treatment that began 20 years ago. Over those years, new treatment principles involving use of drugs alone or in combination were successfully developed for widespread cancers, such as acute childhood leukemia and advanced Hodgkin's disease.

Mr. FLOOD. I told you the Pennsylvania delegation had lunch this afternoon with a spokesman for the University of Pittsburgh. That is an annual thing. Present was your friend, Dr. Fisher of the Pitts-

burgh Medical College. He mentioned the development at that institution of a drug with reference to breast cancer.

Dr. RAUSCHER. This is L–PAM. It is a mustard developed in World War I. We have used it for treating breast cancer.

Mr. FLOOD. How is it administered?

Dr. RAUSCHER. It is an oral pill form, which is one of the reasons it is so widely adaptable to women on the move. These methods were adapted for patients with far advanced cancer of the breast and other solid tumors. Their success in some patients has led to the current interest in applying them to patients early in the course of their disease, especially since 80 percent of breast cancer patients with tumor in the lymph glands at surgery have later developed recurrence, which markedly reduces survival rates.

Mr. FLOOD. Is that prophylactic or curative?

Dr. RAUSCHER. It is prophylactic in a sense that it wards off recurrence of the tumor.

We hope it may be curative as well.

Mr. FLOOD. It will prevent the development of cancer in the lymph nodes?

Dr. RAUSCHER. We hope so and also eliminate recurrence in the other breast.

Mr. FLOOD. Does it follow like night follows day that a cancer in the right breast will produce one in the left breast?

Dr. RAUSCHER. No; that is separate. About 15 percent of the women present with tumors have them in both breasts the first time. But the vast majority are separate primary tumors. If you have a tumor in one breast there is no reason to believe it will automatically show up in the other breast.

Mr. FLOOD. If there is a benign tumor, does it follow that it will become a cancer?

Dr. RAUSCHER. No; it does not. About 80 percent of so-called tumors are benign and they do not ordinarily progress into malignancies.

Mr. FLOOD. Benign tumors are very common.

Dr. RAUSCHER. Very common. It is certainly more common than the cancer.

A study utilizing postoperative treatment with a drug, L–PAM, in patients with positive lymph nodes has shown a significant decrease in recurrences up to 2 years after surgery for removal of the cancer. Since a number of drugs have varying effects in advanced breast cancer, various combinations were tested to improve the results obtained with L–PAM. Preliminary evidence suggests that a three-drug combination is even more effective than L–PAM in patients with advanced cancer.

In summary, as regards breast cancer, we are conducting a multifaceted approach to early detection and treatment tailored to the individual patient. The treatment includes, as appropriate, early drug treatment for subclinical spread of the disease and combined drug treatment for advanced disease. With these new emphases, we are optimistic that a reduction in mortality statistics will be evident within 5 years.

For lung cancer, progress was noted in a large clinical study using cell examination of sputum and chest X-ray to detect lung cancer in symptom-free heavy smokers. In the small group of lung cancers

found to date, about half were too small to be detected by X-ray alone. The cancers appeared to be in early stages, so that 5-year survival of these patients could be higher than the 5 percent expected for patients with symptoms at this time.

In one type of lung cancer, small cell carcinoma, also referred to as osteocarcinoma, a response rate of 50 percent, and some prolongation of survival has been observed with a three-drug combination. This type of cancer constitutes only 10 percent of lung cancer cases in the United States. We have so far had little success in treating the more common types of lung cancer.

Use of an improved flexible fiberoptic colonoscope has greatly improved the capability for locating cancer in the large bowel. It may assist the detection of cancer of the colon in earlier, more curable stages.

CURE OF A CANCER

Mr. FLOOD. How do you cure a cancer?

Dr. RAUSCHER. Either by surgery, radiotherapy, or chemotherapy.

Mr. FLOOD. Other than surgery.

Dr. RAUSCHER. Chemotherapy and radiotherapy are highly effective. The first drug combination that has shown some promise of effectiveness in the treatment of advanced colon cancer has emerged. If this therapy, which is a combination of three drugs given postoperatively is successful, it could make a significant impact on the colon cancer death rate. One of those is Adriamycin that I talked about last year.

Mr. FLOOD. Are there serious aftereffects from these drugs or combinations of drugs?

Dr. RAUSCHER. It depends. Women using L-PAM do not have substantial aftereffects. Adriamycin is a very toxic drug and we have to be very careful how we administer it.

A dramatic improvement was observed in survival of patients with osteogenic sarcoma, a tumor of bone in young people. The 2-year survival rate was increased from 20 to 80 percent, quite remarkably, with the use of a combination of surgery and drug therapy.

Efforts to markedly reduce uterine cervical cancer nationwide continued with a cancer control program of 29 projects established in cooperation with State and territorial health departments.

Mr. Chairman, I would like to list these 29 projects for the record.

Mr. FLOOD. That will be done.

[The list follows:]

CANCER CONTROL UTERINE CERVICAL CANCER DETECTION PROJECTS

At this time, contracts have been awarded to 29 State or territorial health departments:

Arizona
California
Connecticut
Hawaii
Illinois
Kentucky
Louisiana
Maine
Massachusetts
Michigan
Minnesota
Mississippi
Nebraska
Nevada
New Jersey
New York
North Dakota
Ohio
Oklahoma
South Carolina
South Dakota
Tennessee
Texas
Utah
Virginia
Washington
Wisconsin
Wyoming
Trust Territory of the Pacific Islands

PAP TEST

Dr. RAUSCHER. Pap tests are provided to high-risk women who have never, or have seldom, been screened for cervical cancer. Several more projects will be in operation by the end of June, at which time an estimated 500,000 women will have been screened in this program. Not only early stages of cancer, but abnormal changes in the cervix may be identified with the Pap test 5 to 10 years before symptoms of cancer appear, allowing major opportunity for curative treatment, primarily surgery.

Research is also in progress to improve the Pap test because the number of technicians and laboratories presently available are inadequate to conduct the volume of testing required with the existing technique.

Mr. FLOOD. How often should a Pap test be taken?

Dr. RAUSCHER. We recommend it as does the American Cancer Society, in women over the age of 30, once a year for 3 years. Our data now indicate that if those 3 years are negative, it can be less frequent than that the following years.

Efforts are underway to evaluate machines developed for the automated analysis of specimens. The instruments are designed to scan specimens rapidly and select those with abnormal cells for subsequent analysis by trained personnel.

Mr. FLOOD. Can all these tests be administered and results evaluated by paramedics as distinguished from MD's?

Dr. RAUSCHER. The paramedics look for results that are normal. If they are abnormal, they call in the doctors.

LABORATORY RESEARCH ADVANCES

Concurrently with applied cancer research and control activities, basic research in cancer and other biomedical disciplines must be carried out. Increased knowledge of the fundamental nature of cancer will come through research in such sciences as cancer biology and molecular biology.

A major research advance in the area of cancer and viruses was isolation by NCI scientists of a virus from leukemic cells of a patient with acute myelogenous leukemia, a cancer of the white blood cells, which occurs primarily in adults. The virus is immunologically and biochemically similar to the two viruses that cause cancer in nonhuman primates, the gibbon ape and woolly monkey.

While this may be the first successful isolation of a human cancer virus, it should be emphasized that this finding does not indicate that leukemias, or other cancers, are contagious in man either by coughing, sneezing, or any other contact with cancer patients. Leukemias are relatively rare forms of cancer; they occur at random, and have an apparently long latent period. These factors suggest that a complex process is involved in susceptibility to leukemia.

The isolation of the virus is scientifically important because it permits us to take the necessary further steps to identify the one or more factors that cause acute myelogenous leukemia. It also may enable us to develop new approaches to detecting the disease, monitoring the effectiveness of drug treatment, or destroying residual leukemic cells in leukemic patients after drug treatment.

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Immunology research is a heavily emphasized area in cancer investigations. It provides a scientific basis for immunodiagnosis and immunotherapy of cancer, and for monitoring the effectiveness of cancer therapy. In immunotherapy, for example, we attempt to stimulate the body defense mechanisms to destroy cancer cells. In a few short years, knowledge of the basic mechanism of the immune response has increased enormously. Immune responses to antigens on the surface of tumor cells have been demonstrated in animal systems, and there is suggestive evidence that humans respond to antigens specific to their tumors.

As part of the program to develop blood tests for cancer, more than 25 potential immunodiagnostic tests were studied last year with the aid of a bank of stored blood serum specimens. One of the tests used a new purified fraction of carcinoembryonic antigen (CEA), which is a "marker protein" that is increased in the blood of patients with some types of cancer. The test using the purified fraction of CEA was positive in 50 percent of patients with gastrointestinal cancer. This high level of discrimination is an important advance in improving the test for CEA.

Mr. Chairman, this gets to one of the questions you asked Dr. Lamont-Havers this morning: Are there new tests applicable throughout the country? This is one of those.

CANCER CONTROL PROGRAM ACTIVITIES

Our cancer control activities, which are now reaching all corners of the United States, are conducted through demonstrations, communication, and education. Most States have cancer control projects within their borders. The projects are organized to assure active involvement of medical schools, medical and dental societies, community hospitals, physician and volunteer community cancer groups, and the public. Activities are closely coordinated with the related activities of other Federal agencies and State and local governments.

A newly initiated program demonstrates and promotes the use of cancer control in a concerted manner in selected communities. We are working with a number of communities, each of which will mobilize resources of people, facilities, and funds to bring into full use a spectrum of cancer control techniques in prevention, detection, diagnosis, treatment, rehabilitation, and continuing care. We shall have a system for mobilizing all the competences and resources of a community to focus on reducing the cancer problem.

In cooperation with the comprehensive cancer centers, we funded nine projects to undertake planning and development of programs to extend cancer control efforts to community hospitals, practicing physicians, and the general public. In fact, with the stimulus of the new national emphasis on increased awareness of cancer among people, all the comprehensive cancer centers are embarking on such activities.

There are 17 of these centers at the present time. For example: In upstate New York, a traveling oncology team discusses recent advances in cancer medicine and reviews cancer cases; in the Miami area, a series of some 60 free cancer lectures are made available to local hospitals or health agencies; and in Rochester, Minn., a newspaper publishes a weekly column, "Cancer Answers."

A comprehensive cancer centers communications network is being developed to provide regional information and education programs both at the lay and professional levels. Each center will have a communications office whose activities will include a telephone response system and compilation of a directory of cancer services available in the region. Each center will coordinate its communication program with the local American Cancer Society and other cancer-concerned organizations such as health departments.

Activities planned for 1976 include continued interest in identifying individuals at high risk to cancer. We are also funding program activities in education in cancer nursing, training of physical and occupational therapists, rehabilitation research, and psychosocial rehabilitation. Some of the projects demonstrate patient rehabilitation service systems that provide medical, psychosocial, and social support to cancer patients.

ETHNIC GROUP VARIANCES

Mr. FLOOD. In the matter of high risk to cancer, are there ethnic problems?

Dr. RAUSCHER. There are differences in incidences in ethnic groups. You are quite right. That is one of the key clues we have as to the environmental impact on cancer as well.

COMPREHENSIVE CANCER CENTERS

One of our major approaches to a coordinated national program is the establishment of comprehensive cancer centers. We have moved ahead in this program with the recognition of 5 additional centers, bringing to 17 the number currently recognized. Mr. Chairman, I would like to provide a list of the comprehensive cancer centers for the record.

[The list follows:]

COMPREHENSIVE CANCER CENTERS

Colorado Regional Cancer Center, Inc., 1655 Lafayette Street, Suite 301, Denver, Colo. 80218.

Duke University, Duke University Medical Center, Box 3814, Durham, N.C. 27710.

The Fox Chase Cancer Center, 7701 Burholme Avenue–Fox Chase, Philadelphia, Pa. 19111; and University of Pennsylvania Cancer Center, Room 264, School of Medicine, Philadelphia, Pa. 19174.

Fred Hutchinson Cancer Research Center (affiliated with the University of Washington), 1102 Columbia Street, Seattle, Wash. 98104.

Georgetown University, The Vincent T. Lombardi Cancer Research Center, Georgetown University Hospital, Washington, D.C. 20007; and Howard University Cancer Research Center, College of Medicine, Washington, D.C. 20059.

Illinois Cancer Council, includes following organizations: Rush-Presbyterian, St. Lukes Hospital, 1753 West Congress Parkway, Chicago, Ill. 60612; The University of Chicago Cancer Center, The University of Chicago, 950 East 59th Street, Chicago, Ill. 60637; and Northwestern University Cancer Center, Northwestern University School of Medicine, Chicago, Ill. 60611.

Johns Hopkins University, School of Medicine, Baltimore, Md. 21205.

Mayo Comprehensive Cancer Center, Mayo Clinic, Rochester, Minn. 55901.

Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, N.Y. 10021.

Roswell Park Memorial Institute, Buffalo, N.Y. 14203.

Sidney Farber Cancer Center, 35 Binney Street, Boston, Mass. 02115.

University of Alabama, Cancer Research and Training Center, University of

Alabama in Birmingham, 619 South 19th Street, Birmingham, Ala. 35233.
University of Miami, Department of Medicine, University of Miami School of Medicine, P.O. Box 520875, Biscayne Annex, Miami, Fla. 33152.
University of Southern California, LAC–USC Cancer Center, School of Medicine, 2025 Zonal Avenue, Los Angeles, Calif. 90033.
The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, 6723 Bertner Avenue, Houston, Texas. 77025.
University of Wisconsin, Wisconsin Clinical Cancer Center, 701C University Hospitals, 1300 University Avenue, Madison, Wis. 53706.
Yale University, Cancer Research Center, Yale University School of Medicine, 333 Cedar Street, New Haven, Conn. 06510.

These centers are forming a nationwide network of geographically balanced institutions whose purposes are to serve as a national resource for basic research, clinical research, and multidisciplinary patient treatment, in addition to community outreach and communication efforts. Before the end of this year, two, and perhaps three, more centers will be identified, extending still further the nationwide accessibility of cancer expertise through effective demonstration and outreach programs. Sometimes patients will be referred to these centers for consultation or special treatment as outpatients. Such patients can expect to travel to a center and return home the same day, since more than 106.5 million people currently live within 120 miles of a center.

We are also working with the Association of American Cancer Institutes to develop common language and practices among the member institutions regarding their patient data. This association is becoming a principal organization for coordinaton among the major cancer hospitals and research institutions in the country. Each center will participate with the community hospitals in its region. We believe that a new group, the Association of Community Cancer Centers, will help the participation of local personnel in combating cancer. This group has expressed an intention to collaborate with each other and with us in building community cancer programs and assuring that new practices in clinical cancer medicine reach the local level, quickly.

COORDINATION IN ENVIRONMENTAL CARCINOGENESIS PROGRAM

The basis for heavy emphasis in environmental carcinogenesis is the premise that in cancer, as in other diseases, prevention offers the best hope for ultimate control. Since a majority of cancers are believed to be environmentally caused, effective prevention might be accomplished by avoiding exposure to causative agents or by protecting against their actions. But causes in as complex a disease as cancer are mostly unknown. They may be multiple and have a latent period as long as 20 to 30 years.

MULTIPLE CANCERS

Mr. FLOOD. Does it often happen that a person, if he does, has more than one type of cancer?

Dr. RAUSCHER. It doesn't happen with any great frequency, but yes, it can happen.

Mr. FLOOD. Why wouldn't it?

Dr. RAUSCHER. We don't really know.

In addition to our NCI program of testing about 450 potentially cancer-causing agents and working to develop a battery of short-term and less expensive test methods, we established an Interagency Colla-

borative Group on Environmental Carcinogenesis, with a membership of 18 Federal agencies. In the last 18 months, the group has provided a forum for discussion of 25 topics of mutual concern relating to environmental cancer.

We also have joint problem-solving and cost-sharing projects ongoing with the National Institute of Environmental Health Sciences, Environmental Protection Agency, Food and Drug Administration, Oak Ridge National Laboratory, other agencies and also other institutes on our own campus in Bethesda.

AEC PARTICIPATION

Mr. FLOOD. I don't see the Atomic Energy Commission mentioned there.

Dr. RAUSCHER. We have six major projects with them. Oak Ridge is one example.

RELATIONSHIP WITH ERDA

Mr. FLOOD. You have this new agency now, anyhow.

Do you have a relationship with ERDA?

Dr. RAUSCHER. Yes, sir.

One example of that is their laboratory at Oak Ridge.

INTERNATIONAL CANCER RESEARCH DATA BANK PROGRAM (ICRDB)

The ICRDB program is now in operation as part of our international activities. To begin with, we have developed a computer-based cancer information system, called Cancerline, in collaboration with the National Library of Medicine. Information on cancer chemotherapy is now available to scientists, and can be obtained to suit the special needs of practicing physicians. Information on cancer-causing agents and clinical cancer protocols will soon be added.

CONCLUSION

Some 500 highly qualified scientists in the country have participated in developing a plan for a balanced total program for advancing the national effort against cancer. In the light of advances made to date and the potential they offer for the future, we are confident that the ultimate control of cancer will become a reality.

APPROPRIATION REQUEST

Mr. Chairman, the request for the National Cancer Institute totals $605,000,000. The new request includes: $147,200,000 for cause and prevention research; $46,990,000 for detection and diagnosis research; $195,400,000 for treatment research; $102,400,000 for cancer biology; $22,241,000 for cancer centers support; $21,552,000 for research manpower development; $22,637,000 for construction; and $46,580,000 for cancer control.

I shall be pleased to try to answer any questions and supply additional information desired for the record.

Mr. Chairman, this concludes my statement.

PROGRAM IMPACT

Mr. FLOOD. Doctor, all that being true, what is the impact on your program of the reduction in the budget levels from $691 million in 1975 to $605 million in 1976?

Dr. RAUSCHER. In general it will mean a slowing down of ongoing activities. Secondly, it will mean that we will be unable to start new activities until we can reprogram existing dollars which takes 2 to 3 years, as you know. Mr. Chairman, for the record, I will provide additional information regarding the impact.

[The information follows:]

IMPACT OF BUDGET REDUCTION

The reduction from $691 million in 1975 to $605 million in 1976 will have a direct impact on the momentum of the cancer program. There will be no deletion of overall cancer programs, but reduced levels in all programs resulting in the termination of projects, reducing the number of awards, and negotiating downward the size of other projects. A total of 2,522 research grants will be supported in 1975 as compared to 1,934 in 1976. The number of fellowship and training grants will be approximately the same for the 2 years (940 in 1975 and 948 in 1976), although there will be a reduction of $4 million. We will be placing additional emphasis on the new National Research Service Award in 1976. In the contract area, 136 less research and development contracts will be supported, and then there will be a reduction of 24 cancer control contracts. It would cost $85.8 million over the $605 million budget to pay all noncompeting grants and contracts. At the current budget level, the Institute will pay 32 percent of National Cancer Advisory Board approved competing regular research grants; we will not pay $23.9 million of noncompeting regular research grants. As reflected in the budget justification, the funds for noncompeting grants will not permit the funding of all noncompeting awards, but only those of the highest priority. Over the past several years, the funding rate has been approximately 60 percent. In order to pay 60 percent in 1976, the cost would be an additional $28.5 million over the total unfunded noncompeting projects of $85.5 million.

The impact of this reduction would affect all components of the regular research grant program from the clinical cooperative groups through all scientific disciplines supported by the Institute. As an alternative, we could pay all of our noncompeting regular research grants. In that case, the percentage of paid approved competing regular research grants would be reduced from 32 to 9 percent. For example, we would pay 10 new regular reseach grants in 1976 compared to 542 in 1975.

In the cancer centers program, no new center grants would be funded, and there would be an overall 25-percent reduction to the recommended levels of support for ongoing cancer center grants. Exploratory projects, which are an important part of the centers program, would also be reduced or selectively terminated at the 1976 budget level.

The impact of a reduced level would also be felt in the other grant programs, including task forces (bladder, prostate, large bowel and pancreas), radiation development program and clinical education program.

There would also be diminished efforts in the more targeted programs of the Institute, including the lung cancer and breast cancer task forces. Efforts will be reduced in all of the research thrust areas of the budget: cause and prevention research including virus research, chemical carcinogenesis research, nutrition and smoking and health; detection and diagnosis research, including the tumor immunology program; treatment research including that at the cancer centers, combined modality research and drug screening; and cancer biology including the understanding of the fundamental mechanisms of metastasis from concerous cells and the acquisition of knowledge of biological, physical and chemical properties of cell surfaces.

In the area of cancer control, projects in the Community Based Cancer Control Program and the Community Hospital Oncology Treatment Program which are ready for implementation will not be supported at the reduced funding level. Additionaliy, there will be cutbacks in ongoing programs including those in breast and cervical cancer.

CANCER STATISTICS

Mr. FLOOD. Do you have an estimate of how many people in the United States have cancer of any kind, round figures?

Dr. RAUSCHER. There are 665,000 new cases per year.

Mr. FLOOD. That is the second question. How many do you estimate have cancer of any kind in the United States today?

Dr. RAUSCHER. The figures are about 3.5 million.

Mr. FLOOD. How many people who do not have cancer today will have it a year from now?

Dr. RAUSCHER. We expect another 665,000 new cases this year.

Mr. FLOOD. You are not surprised that I asked you that question?

Dr. RAUSCHER. No. It is of great concern to all of us. The thing I worry about is that a dollar cut of this magnitude will have a very definite effect on the momentum of the program that has been built up over the last few years. It is quite serious.

NONCOMPETING GRANTS

Mr. FLOOD. Part of this $86 million reduction is offset by the fact that some of the grants you funded in fiscal 1975 will reach their completion in 1976, correct?

Dr. RAUSCHER. That is right.

Mr. FLOOD. How much money are we talking about with that situation in mind?

Dr. RAUSCHER. We are talking really about the termination of noncompeting grants. That would be about $50 million.

Mr. FLOOD. Your own justification documents state that only the highest priority of noncompeting grants will be funded in fiscal 1976. How much more money do you need in order to honor all of your noncompeting grant commitments? By the way, before you answer that, suppose you tell us what is a noncompeting grant commitment?

Dr. RAUSCHER. Grants are ordinarily awarded, the regular grants, are awarded for a 3-year period. But we only pay 1 year of the award out of any fiscal year. Since we keep them going for 3 years, this incurs a moral commitment to fund them for 2 more years. So we call them noncompeting for the remainder of those 2 years. Now, $24 million would be needed.

Mr. FLOOD. If we were to restore your budget to the 1975 level, can you tell us about how many new grants you would be able to award next year? In this case I am talking strictly about projects that would receive money for the first time and not about grants which are converted for competing status, as you say, to noncompeting status.

Dr. RAUSCHER. I understand.

It would be about 542 new grants at the 1975 level.

HIRING FREEZE

Mr. FLOOD. What is the impact of the NIH hiring freeze on your program?

Dr. RAUSCHER. I think, as Dr. Stetten and Dr. Lamont-Havers said this morning, it is very serious. We have new missions. We have had substantial new funds in the past several years, but inadequate manpower increases, I think, to do the job as well as we could.

CANCER SURVIVAL

Mr. FLOOD. A few minutes ago we were talking about the number of people who have cancer and the number that will have it in the next year, the new ones. Has there been any appreciable improvement in cancer survival rates in the last 10 years?

Dr. RAUSCHER. In the last 10 years there have been major improvements in most of the major cancers with the exception of lung and colon cancer.

As I indicated in my statement, even lung, colon and breast are beginning to show very definite signs of improvement.

Mr. FLOOD. When are we going to see any results? We have been at this quite a long time.

Cancer has been in front of this committee and everywhere else for a long time. When will we see some results of all the cancer research we have supported in the last 5 years in terms of the improved survival rate?

Dr. RAUSCHER. The cancer control program, as you know, was authorized by the Congress in 1971. It really got off the ground in a full way in 1973.

In order for me to go to physicians in any part of the country and say, "use this treatment because it is better," they will say, "Show me your 5-year survival data."

So I think it will be 1978 before we can show an across-the-board substantial improvement in treatment. In the meantime more and more people this very day are receiving better treatment than they did just a year ago.

Mr. FLOOD. You speak of the number and different kinds and forms of cancer. To follow that up, which forms of cancer over this same next 5 years do you expect a marked improvement in the survival rate?

Dr. RAUSCHER. We expect an improvement in all forms of cancer.

Mr. FLOOD. I mean marked improvement in the next 5 years?

Dr. RAUSCHER. Hodgkin's disease, leukemia in children, and breast cancer, with the L-PAM treatment, will show marked improvement in survival.

FREDERICK CANCER RESEARCH CENTER

Mr. FLOOD. To discuss very briefly, with the research over at the Frederick Cancer Research Center, how much money are you investing annually in Frederick Center?

By the way, is that a contract at the Frederick Center?

Dr. RAUSCHER. It is a government-owned facility operated by a contractor.

Mr. FLOOD. Who is the contractor?

Dr. RAUSCHER. Litton Bionetics, Inc., is the contractor. That program is going very well. It started 3 years ago at a level of about $6 million and the current annual level is $25 million.

Mr. FLOOD. What is special about the program?

Dr. RAUSCHER. We are taking advantage of the unique biocontainment facilities there, specifically in relationship to growing viruses. The virus I mentioned in my statement is now being grown there under safe and, I think, effective production conditions. Many of

the chemicals that you and I have been reading about in the environment, such as asbestos and vinyl chloride, are being tested there.

We are producing animals of predigreed varieties for our laboratories in Bethesda as well as all over the country. We have a very new immunology program and cell kinetic program. It is a basic research laboratory of excellence where if there is a research breakthrough which we think is important, we can bring people in from maybe 10 different laboratories throughout the world, house them there and get them to rub elbows and try to solve a common problem.

Mr. FLOOD. Why did you put it there?

Dr. RAUSCHER. Because it happened to be there.

Mr. FLOOD. What was there?

Dr. RAUSCHER. The safety equipment happened to be there already.

Mr. FLOOD. How did that happen?

Dr. RAUSCHER. As you know, it was a facility for biological warfare development some years ago. Since the policy of the country is to no longer support that activity, fortunately it was turned over to the cancer research program.

Mr. FLOOD. I can think of 434 people who will ask me that question when I get to the floor.

CANDIDATE HUMAN VIRUS

We have seen a lot of articles about the possible isolation of what you call candidate human virus. Can you tell us what are the implications of such a finding?

What is a candidate virus?

Dr. RAUSCHER. It is a virus that has been isolated from certain disease tissues, perhaps cancer; therefore, it may be causative of that cancer.

Until further tests are done, we call it a candidate because it has not been proven yet.

Mr. FLOOD. What are the implications for the American people?

Dr. RAUSCHER. We talked about high risk before. For the first time in leukemias we may be able to use that virus to determine whether other so-called normal people are infected with the virus and if they are, whether they are, therefore, at high risk to getting that disease. It ought to help us diagnose their diseases or their risk to diseases much earlier. It might even help in treatment through immunotherapy of existing cancer patients.

COMPREHENSIVE CANCER CENTERS

Mr. FLOOD. Last year you told us that by the end of fiscal year 1975 one-half of the population in the country would be within 60 to 120 miles of a comprehensive cancer center.

Dr. RAUSCHER. Yes, sir.

Mr. FLOOD. Have you achieved that goal?

Dr. RAUSCHER. There are about 106 million Americans now who live within about 120 miles of one of the 17 centers. I'm told that it may take as many as 30 to 31 centers to get about 180 million Americans covered.

Mr. FLOOD. Well, there they are. What are your plans for extending this service to the other half of the population.

Dr. RAUSCHER. We have at least 10 other institutions that are striving to attain recognizable status as a comprehensive center.

Mr. FLOOD. What will be the impact, if any, of this new Health Planning and Resources Development Act on the expansion and creation of these new comprehensive cancer centers?

Dr. RAUSCHER. I think it is going to be a great help to these other programs as well. These are centers that were not built from the ground up. These are established centers of medical excellence, part of which is excellence in cancer. So, in our recognizing them for their expertise in cancer, they are also able to upgrade their staffs that will care for people with cancer, as well as other diseases. I think it will be a great help.

COLLABORATIVE EFFORTS

Mr. FLOOD. By the way, you did mention this to a certain extent, but how does your outfit, the Cancer Institute, relate to the Federal agencies, all Federal agencies whatever they are, that have responsibility for the actual delivery of health care? How do you tie in?

Dr. RAUSCHER. We are in virtual week-to-week contact.

Mr. FLOOD. It used to be like that. They used not to talk to each other.

Dr. RAUSCHER. People from these agencies serve on our review committees in the cancer control program, for instance.

Mr. FLOOD. You are respectable now, is that it?

Dr. RAUSCHER. I think so.

COMPREHENSIVE CANCER CENTERS

Mr. FLOOD. A lot of concern has been expressed that the designation of these comprehensive cancer centers implies some kind of a long-term, and perhaps preferential, support from the Federal Government for maintaining these centers. Do you want to comment on that?

Dr. RAUSCHER. Yes, please.

Mr. FLOOD. I don't blame you.

Dr. RAUSCHER. The only money unique to these comprehensive centers is what we call core support. Funds totaled about $14 million last year. About $150 million in fiscal 1974 went to comprehensive centers. All of that money was competed for through the peer review system on grants and contracts.

They do not have an edge on the market. If they do not compete well, they will not get any money. They must compete as well as any other institution.

CANCER CONTROL

Mr. FLOOD. This budget you are talking about imposes a reduction of almost $5 million in cancer control activities. The goal of that program, as we understood it, was to bridge the gap between research and the application.

It certainly seems very, very important to us. What is the immediate impact of this reduction?

Dr. RAUSCHER. The rationale behind the use of cancer control funds is the short-term use of seed money where we go to a certain State and

say, "Let's set up a breast cancer control project, and you show us how to use that money for something that was not covered at the time, for the same project or a different project." So we hope to have great flexibility with the dollars.

New projects in the intervention areas of Pevention, Detection, Diagnosis and Pretreatment Evaluation and Treatment, Rehabilitation and Continuing Care could not be supported. Included are many projects ready for implementation in the community-based cancer control program and the community hospital oncology treatment program. Additionally, cutbacks will have to be taken in ongoing efforts.

Mr. FLOOD. What results have you had?

Dr. RAUSCHER. Breast cancer detection clinics, I think, is a superb example. Seventy-seven percent of women proven to have cancer are free of cancer in the axillary nodes. We will have a lot of healthy women walking around this country who would have died.

Mr. FLOOD. How many in the next 5 years?

Dr. RAUSCHER. Well, about 1 million.

INCREASE IN TRAVEL

Mr. FLOOD. On page 10 of your justifications, we see a substantial reduction—and I mean substantial—in project contracts and grants. However, you are proposing a very substantial increase in travel, a 20 percent increase in travel. How do you explain that particular increase in light of the fact that you have a reduction in grants, a reduction in contracts, but up goes travel 20 percent. How does that add up?

Dr. RAUSCHER. A full half of that is for ambulatory care. More and more cancer treatment can be done on an outpatient basis. It is cheaper to us and cheaper to the patient to do it that way—not reserving a hospital bed.

Mr. FLOOD. You may want to develop that for the record. That stands out like a sore thumb. You had better provide for the record a detailed analysis now of how that amount of $3,419,000 for travel was computed.

[The information follows:]

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National Cancer Institute - Travel Analysis

The 1976 estimate for travel of $3,419,000 reflects an increase of $519,000 over the 1975 level of $2,900,000.

Of the increase of $519,000, approximately one-half ($260,000) is directly attributable to patient travel for the Institute's Special Ambulatory Care Programs. This increase is necessary to support the costs of travel and lodging of cancer outpatients and escorts during the period of research at the NIH Clinical Center. This research includes programs in surgery, radiation, dermatology, immunology, medical oncology, pediatric oncology and breast cancer. Of the remaining increase ($259,000), $85,000 is associated with the increased travel costs related to the monitoring and evaluation of contract and grant activities in all facets of the National Cancer Program, including those of immunology, breast cancer, carcinogenesis, cell biology and viral oncology. The balance of $174,000 includes expenses attributable to the permanent change of station of Public Health Service Commissioned Officers as well as selective employment of scarce category personnel; travel costs for the training of personnel in activities related to their work requirements; costs for travel to selected cancer meetings, attendance at which is essential to assure that the latest findings of cancer research and control are related amongst world-wide cancer investigators; and travel expenses associated with the Advisory Committees established by the National Cancer Program.

Efforts have been made and are continually being made to hold travel costs to the minimum. In this regard, efforts include: reduction of the number of NCI participants on site visit teams for grants and contract activities; combining site visits in relatively close geographic areas and utilization of conference telephone calls.

The following table reflects the distribution of the National Cancer Institute's travel requirements for both FY 1975 and FY 1976:

(In thousands)

	1975 Estimate	1976 Estimate	Change
Permanent Change of Station.....	30	40	+10
Temporary Duty.....			
Patients & Escorts (Special Ambulatory Care Program)....	1,000	1,260	+260
Training.....	20	32	+12
Meetings.....	350	410	+60
Contract & Grant Monitoring & Collaborative Research Travel.....	1,306	1,391	+85
Consultants & Advisory Committees.....	186	274	+88
Other.....	8	12	+4
Total.....	2,900	3,419	+519

BUDGET INCREASE FOR OTHER SERVICES

Mr. FLOOD. Take a look at page 10 of your justifications. There you are asking for $30,497,000 for other services. What do you mean by other services? An increase of 27 percent in that item is shown there. You are cutting back on all the other things and here is an increase of 27 percent for other services.

Dr. RAUSCHER. I will check this but most of that is because of the very rapid growth of international activities, specifically the International Cancer Research Data Bank.

Mr. FLOOD. But you cannot brush that off with a gesture. Don't you see that? You will be up in the balcony when this goes on the floor and I will be down in the well. Can you imagine them saying, "What about this, 27 percent for other services, and you are going up on travel." That will take some explaining.

Dr. RAUSCHER. It includes communications, data processing and international activities, cancer information dissemination, laboratory alterations and renovations and repairs to equipment.

CURE RATE

Mr. FLOOD. How has the cure rate of childhood leukemia and Hodgkin's disease increased over the past several years? What do you mean by cure rate? Could you discuss the progress that has been made and further improvements you see in the future as applied to these diseases?

Dr. RAUSCHER. In regard to childhood leukemia, before 1960 the reponse to treatment was low and the median survival of patients with this disease was approximately 4 months. Very few children lived beyond 1 year. With the introduction of intensive chemotherapy, the response rate jumped to almost 100 percent—95 percent of the children achieving complete remission (disappearance of all evident disease). The median survival immediately jumped to greater than 2 years. As the programs intensified a plateau appeared on the survival curves which has now reached 50 percent. This means that of all the children who achieve a complete remission half of those children are alive and free of disease at 5 years. Past experience tells us that only an additional 10 percent of these children will probably relapse. So, at the present time, we feel confident that at least 40 percent, and probably more with the newer programs, of all children with childhood leukemia should have long-term disease-free survival tantamount to cure.

A similar situation has occurred in Hodgkin's disease. In 1963, it was considered somewhat revolutionary to say the disease was curable, as was done by a British radiotherapist, Eric Easson. Patients with localized disease at that time had about a 30-percent disease-free survival, while patients with advanced (stage III and IV) were considered invariably doomed to die of Hodgkin's disease. The radiotherapeutic approach improved dramatically and now 10-year data indicate that 70 to 80 percent of all patients with localized (stage I and II) Hodgkin's disease are now expected to remain alive free of all evidence of disease. With the use of combined chemotherapeutic approaches, the response rate of advanced Hodgkin's disease (stages III and IV) dramtically jumped to 80 percent and improved the median survival. As with childhood leukemia, a plateau has appeared on the curve. Half of all the patients who achieve a remission in response to combined drug treatment now are alive, free of disease, off all further therapy and perfectly normal 10 years from the end of therapy.

Mr. FLOOD. The cancer control program is now in its third year of operation. Is NCI getting the research findings out to the community and the physicians? What do you foresee as its role in future years?

Dr. RAUSCHER. Only in the past 2 years has the cancer control program had funding levels which have been sufficient enough to permit major program activities. During this short period of time, the program has been fulfilling its mandate to get research findings to communities and physicians. The program has developed networks of community hospitals and physicians to field test, evaluate and disseminate research findings to selected sites for use in cancer diagnosis, treatment, rehabilitation and continuing care. There are 7 networks for acute childhood leukemia, Hodgkins disease and lymphoma, 12 for breast cancer, and 10 for head and neck cancer. Additionally, there are 12 projects for oncology nursing, 4 for integrated cancer rehabilitation, and 10 in combined treatment modality programs in community hospitals. These are but a few examples of projects directed to community hospitals and community physicians dealing with cancer patients on a daily basis.

In the community based cancer control program, often referred to as the saturation program, our purpose is to involve entire selected communities. Such communities must have a population base of 1½ to 3 million people and must have in operation a population-based cancer data system. This program is intended to produce a coordinated effort of all important cancer groups including medical schools, cancer centers, private physicians, voluntary groups, such as the American Cancer Society, and State and local health departments. The program will decrease fragmentation and by a coordinated effort of cancer control, show a decrease in cancer incidence, morbidity, and mortality.

The cancer control program also sponsors Dial Access and CAN Dial—telephone cancer public information system—telephone services so health professionals and the public can receive up-to-the-minute information on cancer control. Also, in the newly funded communication offices in the comprehensive cancer centers, toll free phone access will be available to the public and health professionals in all 50 States.

As a backup to the regionalized service, the NCI is planning to establish a national WATS line. Even without this, the volume of public inquiries serviced by NCI has mushroomed during the past year as NCI's Office of Cancer Communications has made a concerted effort to reach a wider audience. Individually written letters in answer to inquiries have jumped from an average of 235 letters per month in the last 6 months of calendar year 1973 to 1,230 per month in the last 6 months of calendar year 1974. Telephone inquiries from the general public jumped from 230 per month in the latter half of calendar year 1973 to 800 per month in the last 6 months of calendar year 1974. Most of these inquiries were from cancer patients or their families seeking assistance or treatment.

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posium, and a summary of the task force findings was widely circulated to many other members of the public and the health professional community. NCI worked with many television and radio programs to disseminate the information, and it promoted the use of its publications on breast self-examination and on breast cancer in general.

NCI also conducted a variety of communication activities to promote the dissemination of cancer information. The latest advances in cancer treatment and rehabilitation were publicized by a joint conference for practicing physicians that the NCI cosponsored in November 1974 with the American Cancer Society. The NCI also distributed during the year nearly 2 million copies of a general information pamphlet, "Cancer: What to Know—What to Do About It," through a supermarket distribution system on the east coast. The pamphlet was translated into Spanish and will soon be distributed to Spanish-speaking consumers. Other publications for the general public include a series of 13 organ-site information pamphlets, which have been updated and will be issued early in 1975. A half-hour film, "Progress Against Cancer," is being distributed across the country. In October alone it was telecast 35 times to an estimated audience of 1,200,000.

CANCER TREATMENT

Mr. FLOOD. Have there been recent advances in the treatment of the more common types of cancer? If so, what are they and what is their implication for the future?

Dr. RAUSCHER. In the first 50 years of this century, the effort of cancer therapists was devoted to improving surgery and radiotherapy techniques for all localized cancer. This was done and the survival rates for cancer improved dramatically. However, in the 1950's it became evident that local forms of treatment were not enough and drugs were developed to destroy circulating cancer cells and established metastases. More recent developments indicate that immunotherapy may become an additional effective form of "systemic" treatment. The successful application of these approaches in patients with advanced disease such as Hodgkin's disease, acute leukemia, choriocarcinoma, histiocytic lymphoma, rhabdomyosarcoma and others has now led to their use in the postoperative period in patients who have just had surgery or radiotherapy as their primary treatment. Many of these patients appear to be free of disease but are known to have a high-risk of recurrence. This premise, that adjuvant or systemic treatment at the time of surgery or radiotherapy will improve the cure rate, is being tested in breast cancer, colon cancer, ovarian cancer, head and neck cancer and pancreatic cancer. The early results in breast cancer—a very common disease in women—are very encouraging, indicating that the survival should be markedly improved in the next 5 to 10 years. We now have a lead to pursue in colon cancer since for the first time an effective systemic treatment appears to have been developed at the Mayo Clinic under contract with the National Cancer Institute in the past year. We have similar leads in ovarian cancer. Ovarian cancer is the fifth commonest cancer killer in women and the commonest gynecologic cancer killer in women. Colon cancer is the second commonest cancer killer in the United States. Pancreatic cancer is rapidly increasing and is already fourth on the list of cancer killers.

Mr. FLOOD. What is NCI doing in the area of environmental carcinogenesis? Is NCI cooperating with other Federal agencies in this area?

Dr. RAUSCHER. Efforts are underway to identify and describe environmental agents as well as those associated with occupational exposure. A data base exists for those substances where bioassay indicates a carcinogenic response in animal systems. Epidemiological studies provide clues as to the responses seen in man. Relevant information is also sometimes available from such agencies as the Environmental Protection Agency, the Food and Drug Administration, the Fish and Wildlife Service, and the Energy Resources and Development Agency, to name but a few. A crosswalk between all these resources must be established in order to better define the carcinogenic hazard to man.

The National Cancer Institute has assisted other Federal agencies in numerous areas. To cite a few specific cases:

1. Much attention has recently been focused on municipal water supplies. Close cooperation has been maintained with the Environmental Protection Agency and local and State health departments in an attempt to assess the carcinogenic risk to man from his drinking water.

2. A program is underway with the Department of Transportation to assist them in the identification and classification of chemical carcinogens which pose a hazard to transportation workers involved in accidental spills in railroads, highways, or shipping points.

3. Associated with newly developed technologies in the Federal energy program is a potential health hazard arising from a potential proliferation of pollutants emitted into the atmosphere, water supply, and food chain.

The National Cancer Institute has established the Interagency Collaborative Group for Environmental Carcinogenesis with 18 Federal agencies or subagencies. The group has become a means for alerting member agencies to problem areas regarding environmental and occupational carcinogens.

During the past 12 months, the following subject areas were considered: Experimental and epidemiological studies on arsenic; carcinogenic biorefractories in drinking water; marine animal neoplasms occurring in various waterways and their association with pollution in fish and water; data correlation on mutagenesis and carcinogenesis from various programs using in vivo and in vitro approaches; the role of ultraviolet radiation in terms of skin cancer; the effect of SST travel, and influence of fluorocarbons and ozone on UV penetration of the atmospheric screen; laboratory standards for carcinogens; approaches to cancer etiology and control; consideration of structural analogs to vinyl chloride including vinylidene chloride; reevaluation and updating of critical problem areas such as arsenic, asbestos, and transshipment of carcinogens; cancer epidemiology and man, the third national cancer survey, county-by-county analysis of mortality data, the national death index, and the veterinary medical data program.

Several sub-task groups have been formed to give special attention to topics such as bioassay protocols and guidelines used by NCI and other Federal agencies; development of common definitions and terms

used both by NCI and other Federal agencies, particularly those with a regulatory mission; and means for problem identification and resolution relevant to environmental cancer. Interfacing with trade associations and industries has been intensified. Information on chemicals on bioassay or those to be tested in the future in exchanged with these organizations in order to broaden our data base.

CANCER CONTROL GROUPS

Mr. FLOOD. What steps is NCI taking to involve voluntary cancer control groups, national and community, in its cancer control program and thus create the possibility of minimizing Federal funding for cancer control in the future?

Dr. RAUSCHER. The Institute's cancer control program is attempting to identify and mobilize many resources to provide long-term, non-Federal support for its activities. This effort involves a search for support among voluntary cancer control agencies, other agencies of the Federal Government, and from local, private, and public sources. The cancer control program has clearly stated that its sponsored projects must become self-supporting. Cost sharing is an important feature of many new projects. For example, the 27 breast cancer detection demonstration projects are being cofunded with the American Cancer Society. Also, in the "saturation program," communities must participate on a 50–50 matching funds basis as their programs become fully operational. A subcommittee of the Cancer Control Advisory Committee has been established to examine the whole question of self-support and to look at the issue of matching funds. This subcommittee will provide guidance to cancer control contractors and grantees as to possible sources for such matching funds in their local communities.

ASSOCIATION OF COMMUNITY CANCER CENTERS

Mr. FLOOD. We have recently heard reports in the press about a group of practicing physicians who have organized the Association of Community Cancer Centers. Is there any present or planned relationship between NCI and this group?

Dr. RAUSCHER. Yes. The Association of Community Cancer Centers recently held a meeting in Alexandria, Va., at which personnel from the NCI's cancer control program participated. This meeting was designed to explore the working relationships of the various organizations involved in cancer research and control. The association has an ongoing project to look at community capabilities for clinical research and field testing. Also, by early 1976, the association will have a project sponsored by the cancer control program to determine the most effective means for utilizing the communities' capabilities for the dissemination of information to the public and health professionals.

COMPREHENSIVE CENTERS

Mr. FLOOD. Comprehensive centers remain an integral part of the national cancer program. How many of these centers are needed, what are the future goals of this program, and how does the sharp reduc-

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tion in funding in fiscal 1976 as compared with fiscal 1975 affect the planning and realization of these vital centers?

Dr. RAUSCHER. To date, more than 20 institutions have indicated to the National Cancer Institute that they are planning to develop the wide spectrum of cancer activities, including community involvement; multidisciplinary research, training, and education; patient care units; and detection and demonstration programs, which are necessary to fulfill the goals of a comprehensive center. To date, 17 such centers have been recognized. By the end of fiscal 1976, we anticipate that an additional three or four of these institutions will have developed the characteristics of comprehensive center programs. It is expected that a total of 30 to 31 comprehensive centers are needed to effectively permit nationwide accessibility of cancer research findings and demonstration techniques.

A number of other cancer centers across the country are inaugurating or expanding cancer programs with somewhat more specialized functions, which are nevertheless extremely valuable and indeed essential links in the nationwide network of centers. These centers have a variety of special capabilities such as outstanding excellence in basic or clinical science areas which have recently come to the fore as highly promising research fields such as immunology, unusual and highly specialized facilities such as those needed for fast neutron therapy, unusual and unrecoverable resources for investigations in such areas as cancer epidemiology and nutrition, and a commitment to community outreach programs among populations at a significant distance from established cancer centers.

The reduction in the program would, quite obviously, result in a slowdown of the cancer efforts fostered through these centers. As can be seen from the justification, cancer research centers themselves reflect a decrease of $15 million. An additional $23.8 million will be required to pay all noncompeting continuation costs of cancer center grants in 1976. We will, of course, continue within allowable resources to develop future plans to maintain as well as expand this important segment of the cancer program.

Mr. FLOOD. Mr. Natcher.

CANCER DRUGS

Mr. NATCHER. Doctor, from time to time we read articles in magazines and newspapers concerning certain types of drugs that some people want to use insofar as cancer is concerned.

During the year Members of Congress receive sometimes hundreds of letters in regard to a certain prescription or a drug that they believe should be approved as far as the National Cancer Institute is concerned, and used. What do you do in these cases, Doctor? How do you handle these matters?

Dr. RAUSCHER. We respond to each of them individually. Depending on the drug they are asking about, we provide all the information we have or for that matter, that the American Cancer Society has. In almost every case when we get letters like this we have already tested the drug. We like to point out that there either is or is not any activity relative to other drugs and there are now 42 of them in use by the clinical oncologists.

In some cases there are drugs people feel very strongly that we should approve. In those cases we try to point out in a sympathetic but factual way, that after exhaustive tests there is no evidence of any value of this particular drug in animal systems or, if the drug has been tested by other people, in other countries, we try to get hold of that information, evaluate it, and provide it also to the inquiry.

Mr. NATCHER. One of the drugs we have heard quite a bit about is used, now in England or France.

Dr. RAUSCHER. BCG is in use in France and England, primarily. That is a very useful drug.

Mr. NATCHER. But it is not approved?

Dr. RAUSCHER. It is approved as an investigational new drug (IND) for experimental use. We are testing it at the National Cancer Institute as well as in most of our comprehensive centers in this country. That drug shows great promise. It does not seem to attack the cancer itself directly, but rather stimulates the immune system to develop antibodies to fight the cancer.

Mr. NATCHER. I have two other questions that will require certain information that you may furnish for the record.

Mr. Chairman, with your permission, I will place these questions in the record at this point. This will require additional information, Doctor, on matters I would like to have placed in the record.

Mr. FLOOD. Without objection, that will be done.

I have a few more questions.

NUTRITION

The Cancer Amendments of 1974 emphasize nutrition programs as they relate to cancer.

What are you doing to implement that amendment of the Cancer Act?

Dr. RAUSCHER. We have a standing nutrition committee now. I have presented a plan already to our National Cancer Advisory Board. It has been approved. Before the end of this fiscal year we will have committed an additional $1 million to $1½ million for new projects. In addition to that, within the next couple of weeks I am going to have printed brochures that we will be able to send to families of leukemic children, for example, giving them the best advice we can as to what nutritionally can be done to aid these children.

INFORMATION DISSEMINATION

Mr. FLOOD. What efforts are you making to insure the effective dissemination of this information on cancer?

Dr. RAUSCHER. We are working directly with the American Cancer Society through their regional offices. Every one of our 17 comprehensive centers now has a mandate to make sure that people in their geographic area have access to the latest information, not only people in general, but the professional health delivery manpower. We have cancer information lines developed with our National Library of Medicine where physicians can get on-line information literally in minutes. Each of the centers has a terminal for this kind of thing.

There is much more I could say to this question, Mr. Chairman. I think we have a very effective information dissemination system.

[The information follows:]

INFORMATION DISSEMINATION

The National Cancer Institute is conducting several new activities to get information about cancer to the public, and to health professionals as well.

At each of the 17 Comprehensive Cancer Centers which have been established, we are creating a communications office as a focal point to which the layman and his physician can turn for information, help and advice. We are supplying each Center with WATS lines, so that the lay public and health professionals in the entire region can call for aid toll free. To assist people in having their health needs served as close to home as possible, we have also developed listings, by city and State, of clinicians involved in NCI programs for use by these Centers' communications offices. The Centers will be responsible for developing a directory of other cancer-related resources in their regions and for promoting the new service. In addition, they will be expected to plan and support other cancer education efforts in their regions, directing these particularly to high-risk, hard-to-reach audiences. The Centers are expected to work closely with other groups—such as voluntary, particularly the American Cancer Society, and State agencies and other medical institutions—in the development of these new services.

These efforts will hopefully, be continually increased over the next year. NCI will coordinate and unify the efforts by the various institutions and agencies engaged in disseminating cancer information and education and identify gaps and areas that need strengthening, and will move to correct the deficiencies.

As a backup to the regionalized service, the NCI is planning to establish a national WATS line. Even without this, the volume of public inquiries serviced by NCI has mushroomed during the past year as NCI's Office of Cancer Communications has made a concerted effort to reach a wider audience. Individually written letters in answer to inquiries have jumped from an average of 235 letters per month in the last 6 months of calendar year 1973 to 1,230 per month in the last 6 months of calendar year 1974. Telephone inquiries from the general public jumped from 230 per month in the latter half of calendar year 1973 to 800 per month in the last 6 months of calendar year 1974. Most of these inquiries were from cancer patients or their families seeking assistance or treatment.

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Mr. FLOOD. Mr. Natcher?

LUNG CANCER

Mr. NATCHER. It has come to my attention that Dr. William Hueper was given the first annual award of the Society for Occupational and Environmental Health, at a conference on occupational cancer that was sponsored by NCI last month. I understand that Dr. Hueper, who is now retired had been with NCI and is considered to be a

pioneer in the field of occupational and environmental cancer, has long been of the opinion that there is multiple causation of lung cancer, and that a public health policy which focuses on tobacco use as the major cause can be a serious mistake in assigning priorities and in allocating resources for research. What efforts are now being made to discover other causes of lung cancer?

Dr. RAUSCHER. Of the millions that smoke not all will develop lung cancer, cardiovascular disease, emphysema, and other smoking-related ailments. Individual susceptibility and some environmental conditions are of obvious significance in determining an increased risk of lung cancer in smokers.

However, in the general population of nonsmokers, lung cancer is a rare disease while it becomes 10 to 20 times more frequent in the smoking population. In asbestos workers who do not smoke, the incidence of lung cancer matches that of the nonsmoker in the general population but in the same miners who smoke the risk of lung cancer is almost 50 times higher.

Moreover, a dose response relationship has been demonstrated in smokers; that is, the amount of cigarettes smoked is directly related to the chance of developing lung cancer. Also, in people who stop smoking, the risk of developing lung cancer decreases progressively.

Overall, it is fair to say that lung cancer causation is multifactorial, requiring primarily a susceptible individual and sufficient exposure to tobacco smoke. Perhaps the susceptibility of certain individuals can be modified, and the National Cancer Institute is sponsoring research in this area, but until this can be demonstrated it appears prudent to reduce the effect of smoking by public education and by developing less hazardous cigarettes for those who continue to smoke against all warnings.

CANCER-CAUSING AGENTS

Mr. NATCHER. Would you please provide for the record a list of all known suspects which may be causally related to the development of different types of lung cancer, cancer of the mouth and throat, bladder cancer, and other cancers.

Dr. RAUSCHER. I will provide that information for the record.

[The information follows:]

CANCER-CAUSING AGENTS

The chemical substances and mixtures that have been found to cause cancer in man are listed below. For hundreds of other substances which have been tested in the laboratory there is evidence of carcinogenicity in rodents. In some instances the evidence for carcinogenicity is strong, whereas in others it is barely fragmentary.

1. beta-naphthylamine
2. benzidine
3. 4-aminobiphenyl
4. 4-nitrobiphenyl
5. chlornaphazine (bis-2-chloroethyl-2-naphthylamine)
6. mustard gas (bis-chloroethyl sulphide)
7. nickel carbonyl
8. diethylstilbestrol
9. bis(chloromethyl)ether
10. vinyl chloride
11. aflatoxin
12. asbestos
13. arsenicals

14. chromates
15. estrogenic compounds
16. tobacco
17. tobacco smoke
18. soots
19. tars
20. pitches
21. asphalts
22. cutting oils
23. shale oils
24. creosote oils
25. high boiling petroleum oils
26. coke oven effluents
27. various combustion products
28. betel nut (chewing)
29. radium [1]
30. thorotrast [1]
31. uranium ores [1] (radon and radon daughters)
32. other radioactive materials [1]
33. auramine
34. magenta
35. isopropyl oil
36. wood dust

Mr. FLOOD. Mr. Stokes?

OCCUPATIONAL HEALTH RISKS

Mr. STOKES. I have been informed that a recent study has found that migrants, in particular black migrants, have an increased risk for lung cancer. In a study of Ohio residents, white males born in the South had a 50 percent excess and nonwhite males 100 percent excess, compared to those born in Ohio. Yet there was no difference in the lung cancer rates of black and white Ohio-born males.

The factors implicated in this excess risk were influences of early years of life and exposure to adverse industrial environments subsequent to migration. For example, an analysis of steel workers showed that 33 to 35 deaths from lung cancer occurred among men born in the South. The authors believe that lung cancer, at least among the blacks, may be largely a result of migration and occupational exposure to chemical dusts and fumes in the industrial employment.

Could you comment on the greater occupational health risk of black workers compared to white workers and provide for the record any data you have on a breakdown of employment by race in occupations at risk?

Dr. RAUSCHER. While the study to which you refer is interesting, it is the only one of its kind of which we are aware. NCI scientists have expressed some concern about the validity of this study and the fact that it has not been replicated. We have, however, conducted several studies which indicate that black migrants in certain occupations are at excess risk to lung cancer. We believe that this is attributable to the lack of training and lower socioeconomic status of such individuals which results in their employment in the more hazardous, less pleasant, jobs. We do not have data on employment by race in occupations at risk. We believe that the association is primarily by occupation and that association by race is an artifact.

[1] Carcinogenicity due to radiation.

SMOKING AND HEALTH

Mr. STOKES. There seems to be considerable disagreement as to the role of smoking as contrasted to occupational hazards. On the one hand, large smelting and refining companies tend to point to smoking habits among their workers as the reason for lung cancer while considerable research also shows that the physical proximity to and working conditions at such metal smelters is extremely significant. Would you please comment on the extent to which occupational and industrial factors should be considered major causes of cancer? Is there any type of cancer which appears only in smokers or in nonsmokers?

Dr. RAUSCHER. Some occupational hazards are known determinants of lung cancer, but because of the relatively small populations of workers exposed their significance to the total incidence of lung cancer in our society is very small when compared to the pervasive population exposure to cigarette smoking.

The risk of mesothelioma, a rare form of cancer, is increased among asbestos workers whether smoking or not, but the risk of lung cancer in the same workers is dramatically increased only in those who smoke.

Smoking uranium miners appear to be at a higher risk for lung cancer.

Smelter workers who smoke are at higher risk of lung cancer than the general smoking population of comparable demographic characteristics, indicating that this occupational hazard contributes to the risk. However, in many occupational groups it is difficult to distinguish real occupational risks because the rare nonsmoking workers cannot provide sufficient numbers for clear-cut conclusions.

Other occupational hazards are known or suspected carcinogens: aniline dyes, arsenic, benzene, benzidine, bis-chloromethyl ether, vinyl chloride and others, to mention just a few. Once known, these hazards are very preventable through removal or worker protection. However, it should be noted again that occupational hazards are not likely to be major contributors to overall cancer incidence in the population, where others widespread factors, such as cigarette smoking and dietary habits, are likely to represent overwhelming causative conditions.

Mr. STOKES. Thank you.

Mr. FLOOD. Mr. Michel?

FEDERAL SUPPORT FOR CANCER

Mr. MICHEL. While the National Cancer Institute has the responsibility for the bulk of the Government's cancer research program, there are other Institutes involved in this area as well as other government agencies such as the Atomic Energy Commission and the Veterans' Administration; are there not?

Do you have data available on the total number of Federal dollars presently being spent on cancer research and related areas, on a government-wide basis?

Dr. RAUSCHER. Yes, other Government agencies are involved in cancer research and their research is considered a part of the national cancer program. Estimates for fiscal year 1974 show a total of $660 million were obligated for cancer research and related programs of the

Federal Government. The NCI obligated $581 million in fiscal year 1974 or about 88 percent of the Federal expenditures for research. The remaining estimated $79 million or 12 percent of the total funds were obligated for the most part in other Institutes of NIH, other DHEW programs, Atomic Energy Commission and the Veterans' Administration.

Mr. MICHEL. What other agencies do have active cancer programs and what is the nature and extent of these programs?

Dr. RAUSCHER. In the Department of Health, Education, and Welfare, in the Public Health Service, the Food and Drug Administration, a regulatory agency, has responsibility for carcinogenic foods and drugs; the National Center for Toxicological Research conducts basic research on the mechanisms of carcinogenesis and develops new tests and procedures; the Center for Disease Control investigates the epidemiology of cancer; and the National Institute for Occupational Safety and Health has a program in the environmental carcinogenesis. Several Institutes of the NIH, besides the NCI, conduct research on various aspects of cancer; for example, virus research of the National Institute of Allergy and Infectious Diseases and brain tumor research of the National Institute of Neurological Diseases and Stroke. The Health Resources Administration has responsibilities for cancer control health manpower development with respect to patient care. The National Center for Health Statistics is concerned with the epidemiology and demography of cancer.

Outside of HEW, the National Science Foundation has programs in basic biomedical research. The Department of Defense and the Veterans' Administration have responsibility for care of cancer patients; that is, the military personnel and their dependents; and also conduct clinical research. The National Aeronautics and Space Administration has projects for application of space technology to cancer patient care and diagnosis.

Among the agencies with regulatory responsibilities, in addition to FDA, the Department of Agriculture has programs on nutrition and diet, animal feed problems, and environmental carcinogenesis, for example, investigation of pesticides. The Energy Research and Development Administration has programs in radiation research, including drugs to enhance the effects of radiation; the Department of Labor's Occupational Safety and Health Administration is concerned with control of occupational cancer hazards in the national work force; the Department of Transportation is concerned with regulation of the transport of chemical cancer-causing agents; and the Environmental Protection Agency with control of air pollution in relation to carcinogenesis. The EPA also conducts some basic cancer research.

Mr. MICHEL. How have these other programs been coordinated with the activities of NCI in the past?

Dr. RAUSCHER. In the past, there have been formal arrangements with other agencies, such as collaborative clinical research with the Veterans' Administration. Other relationships have been more informal in nature, for mutual assistance on problems and exchange of information.

Mr. MICHEL. The Interagency Coordinating Committee, organized to provide coordination of the overall national effort against cancer,

is composed, you say, of representatives of 14 Federal agencies. Could we have a list of these 14 agencies and what their specific interest in the cancer program entails?

Dr. RAUSCHER. The organizations which presently comprise the Interagency Coordinating Committee and their specific field of interests are:

Food and Drug Administration—responsibility for carcinogenic food and drugs (regulatory). National Center for Toxicological Research—basic research on mechanisms of carcinogenesis and development of new tests and procedures.

Center for Disease Control—epidemiology of cancer. National Institute for Occupational Safety and Health—environmental carcinogenesis.

National Institutes of Health—research on aspects of the cancer problem.

National Cancer Institute—cancer research and control.

Health Resources Administration—cancer control health manpower development with respect to patient care. National Center for Health Statistics—epidemiology and demography.

Department of Agriculture—nutrition and diet; animal feed problems; environmental carcinogenesis, i.e., pesticides (regulatory).

National Science Foundation—basic biomedical research.

Department of Defense—responsibility for care of cancer patients, i.e., military and dependents; clinical research.

Veterans' Administration—same as Department of Defense.

Energy, Research and Development Administration—radiation and basic research; some drug research (regulatory).

Department of Labor—control of occupational cancer hazards in the national work force (regulatory).

Department of Transportation—regulation of the transport of chemical carcinogens (regulatory).

Environmental Protection Agency—control of air pollution in relation to carcinogenesis; basic cancer research (regulatory).

National Aeronautics and Space Administration—application of space technology to cancer patient care and diagnosis.

Mr. MICHEL. How many people are actually involved in the program administered through the Cancer Institute, including those involved both intramurally and extramurally?

Do you have any estimates on how many people throughout the Government are directly or indirectly working on the cancer program?

Dr. RAUSCHER. During fiscal year 1975 the NCI had total staff of 1,932 persons including scientists, technicians, administrative, and supporting personnel. NCI extramural programs funded throughout the Nation in cancer centers, research institutes, universities, and public health agencies directly involve nearly 54,000 scientists, technical staff, and supporting personnel on a full- or part-time basis. In addition, cancer related research funded by other Federal agencies supported approximately 16,700 scientists, technical staff, and supporting personnel on a full- or part-time basis.

In summary, approximately 73,000 personnel supported by Federal funds are directly or indirectly involved in cancer research, both intramurally and extramurally.

Mr. MICHEL. What effort has been made in the private sector? Do you have any figures available on how much private money has been invested in cancer programs and how many people are involved in private research? Perhaps you could place a table in the record showing a comparison between the Government and private sector.

Dr. RAUSCHER. Yes, I will supply that information for the record.

[The information follows:]

RESOURCES—FEDERAL AND PRIVATE

RESOURCE COMPARISON OF THE FEDERAL GOVERNMENT TO THE PRIVATE SECTOR AND STATE AND LOCAL GOVERNMENTS FOR FISCAL YEAR 1974

[Dollar amount in thousands]

	Amount	Percent	Man-years [1]	Percent
Federal Government:				
NCI	$581,114	65.1	32,000	66.8
Other agencies	79,000	8.9	9,600	20.1
Total Federal Government	660,114	74.0	41,600	86.9
Private sector and State and local government:				
Voluntary agencies	92,000	10.3	2,486	5.2
Private institutions	40,000	4.5	1,081	2.3
Industry	16,000	1.8	433	.9
State and local government	84,000	9.4	2,268	4.7
Total private and State and local government	232,000	26.0	6,268	13.1
Total resources	892,114	100.0	47,868	100.0

[1] Included in this column are personnel supported through grants and contracts.

INTERNATIONAL CANCER ACTIVITIES

Mr. MICHEL. You mention the establishment of an Office of International Affairs, and I was also reading in a recent NIH publication of the U.S.-U.S.S.R. exchange program which has been established to provide the interchange of cancer research information between the two countries. Do any other countries have cancer research programs and, if so, to what extent?

Dr. RAUSCHER. Cancer research programs exist in almost all the developed countries and many of the developing nations.

The extent of these programs varies from country to country, albeit none is as extensive as the National Cancer Program of the United States. For example, in the Federal Republic of Germany the thrust of cancer research relates to fundamental research in biochemistry, virology, and molecular biology. In the United Kingdom, for instance, we recognize their scientific interests in cancer epidemiology, diagnosis, and therapy as well as cancer control. On the other hand, Israel and Japan are very strong in research in the basic sciences leading to the application of that information to the treatment of leukemia and other cancers.

By means of grants and contracts, NCI supports various projects in foreign countries in which there are unique facilities and resources available and outstanding capabilities and expertise among their scientists. In fiscal year 1974, 24 grants were awarded to scientists in 19 institutions in 10 different countries. Seventy-four contracts funded by NCI are in institutions of 19 countries. The thrust of the research supported by this outlay of approximately $6 million is in

the areas of carcinogenesis and cancer epidemiology; cancer biology; immunology and immunotherapy, viral oncology; chemotherapy and radiation therapy; leukemia, lymphoma, and lung and breast cancer.

As an example of these cooperative projects, the NCI maintains a contract with Uganda's Makerere University College Council for the "Development and Operation of a Lymphoma Treatment Center and a Solid Tumor Treatment Center" in the Uganda Cancer Institute (UCI). The scope of the research program at Uganda Cancer Institute includes the evaluation and treatment of patients with Burkitt's lymphoma and other lymphomas, malignant melanoma, and Karposi's sarcoma.

In the case of melanoma, preliminary studies established that Pasteur Institute BCG, administered by scarification, stimulated cell-mediated immune responses. It appeared that such treatment might have beneficial effects as an adjuvant to surgery in patients whose disease had not spread beyond the regional lymph nodes. More recent followup of the patients in this study revealed that only one of six patients treated with BCG developed recurrent tumor (one year after completion of immunotherapy).

Notwithstanding, of course, is the individual effort of the Soviet Union and that of its satellites. In Poland the thrust is in virology and epidemiology. In Czechoslovakia it is chemotherapy. In Romania it is immunology.

Thus, the National Cancer Institute is actively pursuing cooperative links between the National Cancer Institute-National Cancer Program research programs and parallel international programs. Effective coordination of cancer research is maintained among major international organizations such as the World Health Organization, International Union Against Cancer, International Agency for Cancer Research and Pan American Health Organization which are important resources in terms of membership and experience, and are appropriate mechanisms for international research operations.

Mr. MICHEL. Do you have any statistics regarding the incidence of cancer in other countries? As we all know, cancer ranks as the second leading cause of death in this country. How does this compare with other countries?

Dr. RAUSCHER. With regard to the question concerning deaths caused by cancer in the United States, cancer does rank as the second leading cause of death. Cancer also ranks second for most developed countries, for example, England and Wales, Germany, France, Japan, Sweden, Denmark, and Finland. A few exceptions are noted for Chile and Portugal which have rates for influenza, pneumonia and bronchitis which are higher than those for malignant neoplasms.

With regard to the incidence of cancer, the International Union Against Cancer has compiled incidence data from various cancer registries around the world which meet certain minimum standards of completeness of case ascertainment, accuracy of information, and definition of the population from which the cases arose. The first volume was published in 1966, the second in 1970, and a third is in preparation. There are problems of comparison among the registries, however, as the registries may differ in their definition of tumors to be included or excluded and in the availability of medical care in the community.

I would like to provide a table on cancer incidence rates and explanation of the data presented.

[The information follows:]

CANCER INCIDENCE

The table below presents for various selected registries, the average annual incidence rates based on cases diagnosed during the time periods indicated. The rates are for all cancer sites combined, excluding nonmelanoma skin cancer, and are age-adjusted to the European standard population. Age-adjusting is a statistical method used to account for differences in the age distribution of the populations whose rates are to be compared. Some of the registries included cases of carcinoma in situ of the cervix, as indicated, while most did not. The reported incidence of these tumors depends to a large extent on the level of screening in the community. Whereas data are available for some areas of Africa, the number of cases reported are much smaller than those reported by the European and North American registries and were therefore not included in this table.

The first 10 countries listed are in Europe. The range of rates in Europe for males was from 225.8 per 100,000 population in rural Norway to 345.4 in Hamburg (FDR), whereas the range for females was from 204.4 in Yugoslavia to 297.0 in Denmark. The higher incidence rates of cancer among residents of urban areas compared to rural is shown by the Norway rates: 305.6 vs. 225.8 in males and 253.9 vs. 210.8 in females. The incidence rates in Bombay, India are considerably lower than for any other population shown. The rates for the Third National Cancer Survey, which included seven cities and two States in the United States, are for a more recent time period and may reflect increases in incidence which the other registries had not yet experienced.

The incidence of cancer of specific sites varies greatly among the countries, with different sites having differing patterns. For example, the incidence of lung cancer is high in industrialized, developed nations and much lower in the less developed areas of the world. Stomach cancer rates are high in Japan and low in the United States; a reversed relationship is seen for colon cancer and for breast cancer. A recent NCI publication, Cancer Rates and Risks, uses both incidence and mortality data in discussions of the international variation in rates of specific forms of cancer.

Average annual incidence rates[1] of cancer, all sites combined[2], by sex and country.

	Years	Males	(rank)	Females	(rank)
Denmark	1958-62	292.8	(10)	297.0	(4,5)
Finland	1962-65	345.1	(6)	230.8	(13)
German Democratic Republic	1964-66	261.2	(17)	231.5	(12)
German Federal Republic - Hamburg	1963-66	345.4	(5)	285.0	(6)
Norway - urban	1964-66	305.6	(8)	253.9	(9)
Norway - rural	1964-66	225.8	(19)	210.8	(15)
Sweden	1962-65	285.2	(11)	278.4	(7)
United Kingdom - Birmingham	1963-66	327.7	(7)	247.8	(10)
Scotland	1963-66	294.8	(9)	217.4	(14)
Yugoslavia	1961-65	268.5	(13)	204.4	(17)
Israel - all Jews	1960-66	261.6	(16)	262.7	(8)
India - Bombay[3]	1964-66	198.0	(20)	179.2	(20)
Japan - Miyagi[3]	1962-64	276.0	(12)	195.4	(19)
Japan - Okayama	1966	263.8	(15)	197.3	(18)
Puerto Rico	1964-66	251.4	(18)	204.6	(16)
Canada - Saskatchewan	1963-66	370.0	(4)	317.0	(1)
Canada - Quebec	1963-66	264.9	(14)	244.6	(11)
Connecticut	1963-65	377.0	(3)	307.6	(3)
Third National Cancer Survey - whites[4]	1969-71	389.2	(2)	313.6	(2)
Third National Cancer Survey - blacks[4]	1969-71	453.4	(1)	297.0	(4,5)

SOURCE: UICC: Cancer Incidence in Five Continents, Vol. II, (Doll, R, Muir, C, Waterhouse, J, Eds.) Geneva, International Union Against Cancer, 1970.

[1] Per 100,000 population, age-adjusted to the European population.
[2] Excludes nonmelanoma skin cancers.
[3] Includes carcinoma in situ of the cervix.
[4] Third National Cancer Survey. NCI Monograph 41, 1975.

Mr. MICHEL. What efforts have and are being made to coordinate research data from other parts of the world? Is the retrieval system as good as our own internal efforts?

Dr. RAUSCHER. The National Cancer Institute is deeply involved in the collection and dissemination of cancer research information on an international scale as evidenced by the International Cancer Research Data Bank (ICRDB) program. For example, the ICRDB program has established a Current Cancer Research Project Registry Office which is currently requesting descriptions of current cancer research projects from countries around the world. Contracts are currently being reviewed which will screen all major biomedical journals from many countries, select articles that deal with cancer, and prepare abstracts of the published research results. Efforts are also being made to obtain abstracts of cancer-related papers presented at scientific meetings in countries throughout the world.

The ICRDB program is also negotiating with organizations in Japan, Latin America (with the Pan American Health Organization, PAHO), Russia and other countries to set up satellite centers which will provide a steady stream of data about cancer research results in those geographic areas to the ICRDB program. International centers for collecting worldwide information about cancer epidemiology projects and tumor immunotherapy projects are currently established and operating. Another center for collecting information from many countries on cancer therapy projects will soon receive support through the ICRDB program. A program for stimulating scientist-to-scientist communication through support of brief collaborative research projects and support of international workshops on critical research areas is being negotiated with the International Union Against Cancer (UICC) in Geneva. Discussions with the World Health Organization (WHO) in Geneva will lead to the establishment of a center for exchange of cancer information with developing countries.

All of the data collected by the ICRDB program is prepared for entry into CANCERLINE—a computer data base prepared by NCI using the software/hardware programs located in the National Library of Medicine (NLM). This system is used for on-line searching of the CANCERLINE data base at some 400 computer terminals throughout the United States and other countries. This retrieval operation is the only worldwide cancer information system of its kind. The information is also grouped into various specialized cancer-oriented publications which are distributed to cancer researchers throughout the world.

CURE FOR CANCER

Mr. MICHEL. The Federal Government recognized the importance of this problem many years ago when it established the National Cancer Institute back in 1937. Since that time, a lot of time and money has been invested in finding the cause and cure for cancer, especially in the last 4 or 5 years. Just how much closer are we to really finding a cure for this disease than we were 38 years ago? In which areas of research have we made the greatest gains?

Dr. RAUSCHER. An enormous amount of progress has been made in curing cancer since 1937. First, one has to realize that cancer is not one disease. There are more than 100 different diagnostic categories of cancer and subdivisions within these categories. Between 1937 and 1950 we learned we could cure a fraction of patients with many cancers such as breast, colon and rectum with surgery. As the technology of surgery improved, associated with better anesthesia and antibiotics, and the morbidity and mortality of surgery was reduced, the cure rate went up just from surgery alone. In the same time period, we learned we could cure a fraction of some patients' localized cancers, such as carcinoma of the cervix and some lymphomas, with radiotherapy alone. Again, as radiotherapy technology improved the cure rates improved with better local control and less morbidity to the patient. By about 1950 we also learned that we could not cure all cancers with surgery and radiotherapy alone and the reason for this became apparent. Cancers that appeared localized often were not. Beginning in the 1950's we attempted to develop drugs to supplement surgery and radiotherapy. These drugs were tested in patients with advanced disease. Since that time we have also demonstrated that drugs can cure patients with advanced stages of some cancers and there are at least 10 examples of cancers which can be cured by drugs alone in their advanced stages. About 10 years ago it became apparent immunotherapy would be useful also in controlling some cancer. This type of treatment is now just reaching clinical trial. Potential for increasing cure rates in the next 10 years is great because we now have very effective tools for controlling localized cancers (radiotherapy and surgery). We also have resources to deal effectively with circulating cancer cells and should be able to prevent recurrence in the postoperative period in the remainder of patients not cured by surgery alone in breast cancer, colon cancer, ovarian cancer, head and neck cancers, and other tumors which are present in a local form that have a high tendency of recurrence.

CANCER RATES AND RISKS

Mr. MICHEL. Has the incidence of cancer changed in that time period? Or is the percentage of people suffering from that disease the same as 20 or 30 years ago?

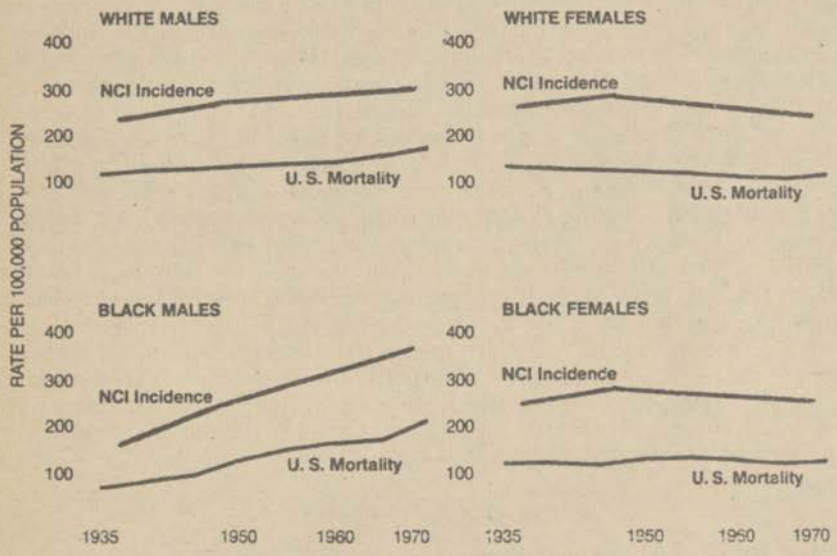
Dr. RAUSCHER. Cancer incidence has declined in women for this time interval, and increased in men (largely due to the cancers related to cigarette smoking). I would like to provide charts which demonstrate the cancer incidence rates for various periods.

[The information follows:]

Incidence and Mortality

Cancer Rates and Risks, 2nd Edition[1/]

TIME TRENDS IN CANCER INCIDENCE AND MORTALITY BY RACE AND SEX: United States, 1935-1970 (age adjusted to 1950).



1/ This publication was prepared by the Biometry Branch, National Cancer Institute. DHEW Publication No. (NIH) 75-691.

TIME TRENDS IN CANCER INCIDENCE RATES, BY SITE, RACE, AND SEX; three surveys conducted by NCI: 1937, 1947, and 1969.

SITE	RACE AND SEX	1937	1947	1969
Esophagus	White Male	7.8	8.3	6.0
	White Female	1.6	1.9	1.6
	Black Male	6.0	9.7	19.5
	Black Female	1.4	2.2	4.2
Stomach	White Male	44.0	34.1	14.0
	White Female	26.1	18.3	6.1
	Black Male	38.3	39.6	20.5
	Black Female	22.2	22.8	10.0
Colon	White Male	22.4	26.2	33.1
	White Female	24.0	27.8	27.6
	Black Male	13.2	13.9	26.4
	Black Female	11.8	16.2	37.1
Rectum	White Male	19.0	22.1	17.3
	White Female	12.2	15.2	10.7
	Black Male	8.0	12.7	13.1
	Black Female	8.4	13.6	9.9
Pancreas	White Male	7.0	9.3	11.3
	White Female	4.9	5.5	6.7
	Black Male	5.0	11.6	15.0
	Black Female	3.4	6.4	14.5
Lung	White Male	13.7	29.5	68.9
	White Female	4.0	6.5	13.5
	Black Male	8.4	25.4	84.7
	Black Female	3.4	5.8	18.2
Breast	White Female	66.2	72.6	75.2
	Black Female	49.4	53.9	67.8
Uterus (Total)	White Female	59.9	56.3	35.3
	Black Female	108.8	95.6	49.0
Ovary	White Female	12.7	14.7	13.3
	Black Female	5.5	9.9	11.4
Prostate	White Male	29.8	34.8	42.7
	Black Male	30.7	49.9	77.6
Bladder	White Male	15.3	18.6	22.5
	White Female	7.4	8.0	5.9
	Black Male	5.6	7.0	15.3
	Black Female	5.5	7.9	4.5

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DOLLARS SPENT ON CANCER RESEARCH

Mr. MICHEL. For the record, do you have available the total amount of money spent to date on cancer research? How much does it take to support 38 years of research?

Dr. RAUSCHER. Obligations by the National Cancer Institute since its inception total $4,131,710,000, which includes $699,378,000 for fiscal year 1975. In addition to these funds administered through NCI, both other Federal agencies and State and local governments as well as private and nonprofit institutions have spent money for cancer research during this period, but, this data is unavailable back to 1938. However, for 1974 the resources for the national cancer program totaled $892,114,000 of which the NCI was $581,114,000, other Federal agencies—$79 million, State and local governments—$84 million, voluntary agencies—$92 million, private institutions and industry—$56 million.

INTRAMURAL AND EXTRAMURAL PROJECTS

Mr. MICHEL. You have broken the cancer program into various areas of research. How many research projects will you fund in 1976 totally, considering both in-house and through outside grants and contracts?

Dr. RAUSCHER. For 1976, projections indicate that an estimated 3,225 projects will be underway by the Institute. Of these projects approximately 1,843 will be funded through grants, 742 through contracts and 640 will be intramural projects.

Mr. MICHEL. Could we have a breakdown, for the record, of the number of projects by objective? That is, how many individual projects are underway just to find the cause of cancer; how many are involved with detection methods, with treatment procedures, et cetera? Could you provide that for the record?

Dr. RAUSCHER. For 1976 there will be an estimated 3,225 individual projects dealing in all areas of cancer research. These projects will be distributed through the research areas of: cause and prevention, 931 projects (or 29 percent); detection and diagnosis, 197 projects (6 percent); treatment, 1,241 projects (38 percent); and cancer biology, 856 projects (27 percent).

SMOKING AND CANCER

Mr. MICHEL. Among the projects mentioned in your justifications regarding cause and prevention research (page 26), I noted an item which included "the investigation of smoking habits and modified tobacco products in order to identify susceptible individuals and develop a less hazardous cigarette". What's this all about? Are we to infer from this that NCI is spending its time and money developing a healthier cigarette?

Dr. RAUSCHER. The National Cancer Institute feels a responsibility toward the nearly 60 million Americans who continue to smoke against all warnings. We approach this smoking habit as a disease, much as alcoholism or drug abuse. This is justified because smoking is a social problem with far-reaching social and economic repercussions. Our

research programs toward reducing the risk of the smoker covers three main approaches. One is the identification of high-risk individuals, second is the development of drugs that may help the individual stop smoking and the third is the development of less hazardous cigarettes.

In the last area it appears entirely feasible that cigarettes of low carcinogenic activity and low risk for cardiovascular and respiratory problems can be developed in the next few years. Thus our message to the smoker is that if he cannot stop smoking, at least he should smoke those less hazardous products we have helped to develop.

This research has been reviewed and approved by the Naional Cancer Advisory Board, the tobacco working group and other advisory groups that this Institute regularly consults, as well as by congressional appropriation committees.

CANCER DETECTION

Mr. MICHEL. In the area of cancer detection, you say in your justifications that annual checkups even to just the older half of the population in whom most cancers occur would overload existing medical facilities.

Do you have any statistics on the percentage of the population who now protect themselves by getting regular yearly physicals?

Dr. RAUSCHER. We estimate that no more than 20 percent of the adult population and probably much less, now receive annual physicals, but we have no firm statistics. We think the figure is slowly increasing, and would like to see it do so more rapidly. On the other hand, physicals for the rest of the adults would take perhaps one-tenth of all doctors' time; if they had this to spare. There are other competing unmet medical needs in the country.

We are therefore attempting to, by research, develop simple screening tests to detect early cancer, blood test for example, which will need little physician time, and to expand the use of other detection procedures such as cytologic screening and X-ray mammography in the cancer control program. We are also attempting to improve those existing methods, this is, by developing automated machines to help read cytologic specimens, and to find ways of doing mammograms with less radiation exposure.

Mr. MICHEL. What do you estimate is the current percentage among the high-risk groups who already have checkups on their volition?

Dr. RAUSCHER. The fraction of individuals exposed to carcinogens who have voluntary checkups is conditioned by their knowledge of exposure and the availability of medical services. In some industrial exposures in large companies nearly all at risk participate in the checkups made available. In other industrial exposures, involving transient workers and many small companies the fraction is much lower. The major nonindustrial high-risk group consists of cigarette smokers. Good medical practice recommends an annual checkup for lung cancer in those who continue to smoke, but probably only a few smokers follow the advice.

From this, and from our tentative figure that less than 20 percent of the general adult population receives regular examination, I made a rough working estimate that less than 40 percent, perhaps much less,

of high-risk groups receive voluntary checkups. We support research and control projects on the early detection of cancer of the lung, bowel, breast, cervix, and pancreas which include participation of geographically limited high-risk groups, defined either by exposure to carcinogens or by less specific criteria such as socioeconomic level and age. These will help develop greater public and professional awareness of the need for regular checkups. We also cooperate with the press in making hazards known, and with the public education programs of the American Cancer Society.

Mr. MICHEL. You say that an estimated 500,000 women will have been screened with the use of Pap tests through 29 cancer control projects by the end of June. What is the total number of women in the high-risk group?

Dr. RAUSCHER. The 500,000 women screened with the Pap test by the end of fiscal year 1975 will be effected through 12 implementation contracts which have been operational for almost 1 year through NCI cancer control projects with State health departments. The remaining 17 projects in fiscal year 1975 will complete planning phases or will be newly funded. Seven more will begin implementation in early fiscal year 1976. It is difficult to estimate the exact number of high-risk women. Important risk factors relate to cervical cancer that is, older age, early parity, socioeconomic factors. The American Cancer Society through a Gallup poll estimates that 78 percent of U.S. women have had a Pap test at some time in their lives and that 52 percent have had one within the last year. The remaining number must be reached but not all of this 22 percent are in the highest risk category. It is estimated that by the end of the current cancer control contract period (3 years) 4 to 5 million women at highest risk will be screened through these projects.

At the present time, it appears that the contractors are reaching the high-risk segments of the population. However, meaningful correlations between known risk factors and the populations being screened will have to await analyses of at least the first year's data. This data will not be available to NCI until the end of fiscal year 1975. Analyses of the first year's efforts will be used as a means of redirecting program emphasis toward the 3-year goal of reaching that segment of the population which have not availed themselves of such preventive medical services.

Mr. MICHEL. At one point, only about 25 percent of the women in this country availed themselves of the various cancer-detecting tests available. Have we been able to improve this record?

Dr. RAUSCHER. According to a recent Gallup poll taken for the American Cancer Society in January 1974, 78 percent of all American women have had a Pap test at least once. This represents an advance from 53 percent in 1970 and from 48 percent in 1964. Also, the proportion of women who reported having had a Pap test within the past year have more than doubled in the last 10 years—up from 23 percent to 52 percent.

In another Gallup study taken in October 1973, conducted for the American Cancer Society on people's attitudes and behaviour toward breast cancer, it was found that one-half of the adult female population do not have annual breast examinations by a physician. The seriousness of the problem of nonexamination is even more severe among

older women, the poorly educated, low-income women, and blacks. It was also found that while 77 percent of women were aware of the benefits of breast self-examination, only 18 percent of all women practiced monthly breast self-examinations during the last year. On the basis of these and other data the NCI will launch efforts in fiscal year 1976 to increase the awareness of the benefits of breast self-examination and to specifically induce a greater proportion of women to practice it regularly.

Mr. MICHEL. Has the development of new methods such as cytologic screening and X-ray mammography aided substantially in the number of women who can be tested, especially in the high-risk groups?

Dr. RAUSCHER. Without the development of simple screening methods such as the Pap test and X-ray mammography, it would be very difficult and costly to examine the large number of symptom-free people needed to detect early cancers.

Cytologic screening for cancer of the uterine cervix is now after some years used broadly in medical practice, and is believed to have reduced mortality from this cancer. Further expansion of its use continues, but its application has lagged in socially and economically deprived groups, who, unfortunately have relatively high rates of the disease. We are trying to correct this through the cervical cancer screening program, started in 1974 and still being expanded, which seeks to reach such high-risk groups by working through State health departments.

X-ray mammography for early detection of breast cancer is a much newer technique. From research we expect that it can reduce mortality when broadly applied. We are fostering this through the 27 ACS–NCI breast cancer detection demonstration units throughout the country. We are making a special effort in the program to reach disadvantaged groups. Since high-risk groups are hard to define for breast cancer, we have not addressed this.

Mr. MICHEL. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Shriver?

Mr. SHRIVER. Thank you, Mr. Chairman.

ENVIRONMENTALLY CAUSED CANCERS

Mr. SHRIVER. Dr. Rauscher, this committee has been told that up to 80 percent of all cancers are environmentally caused. What percent of this budget request is designated for research and treatment of environmentally caused cancers?

Dr. RAUSCHER. Thank you Mr. Shriver. This is a critical question and has to do also with the processes whereby we set priorities in the national cancer program. It is true that scientists in this country and abroad feel, and I believe with good data, that up to 80 percent or more of man's cancers are extrinsically induced. That is, it is not our inherent fate to develop cancer simply because we're people. Most cancers are caused by something we do, we eat, we drink, we smoke. To the extent that this is true, and I believe it is, then we ought to be able to do more about identifying these environmental factors toward inevitable prevention of these cancers in people. Total direct obligations from the National Cancer Institute for identifiable projects in environmental carcinogenesis research for 1974 was $100,200,000 or about 17

percent of the total budget of $589 million (see detailed breakdown attached). In addition to bioassay projects in environmental chemical carcinogenesis, studies include research on resource and time saving methods of performing bioassays as well as directly relatable associated costs of training, cancer control, and construction. Another way to relate the dollars for carcinogenesis to the budget is to compare environmental carcinogensis costs to the cause and prevention research portion of the budget (which totaled $139,315,000 in fiscal year 1974). Based on the total shown or the attached listing, which I will include for the record, of $100.2 million and deducting training, construction and cancer control costs of $11.6 million we have a comparison of $88.6 million for environmental carcinogenesis to the total budget for cause and prevention research. This represents 63.6 percent of the cause and prevention research obligations for 1974.

In addition to the above amounts another approximate $100 million was provided in fiscal year 1974 for studies in very closely related cancer biology. These studies having to do with the varying mechanisms of cancer induction. In other words, if we can determine why cancers occur and how they are induced we may very well be able to develop the means to prevent the cancer process following exposure to environmental carcinogens. In this regard, there are essentially three ways that environmentally induced cancers can be decreased or prevented. In the first two, the role of the National Cancer Institute by law is advisory. In the third, the NCI plays a very direct and leading role.

(1) One can prevent these cancers by cleaning up the environment. While NCI has no regulatory authority for this approach, we do in fact test between 400 and 600 compounds per year so that we are better able to advise the regulatory agencies such as the FDA, EPA, etc. It should be emphasized at this point that to test one compound of the many thousands that may gain entrance to the environment each year requires between 400 and 600 animals treated and examined for up to 3 years and at a total cost of $90,000 per test compound.

(2) Introduce noncarcinogenic substitutes. Here again through its testing program, NCI is able to advise the regulatory agencies as to which compounds may have lower or virtually no carcinogenic impact on people.

(3) Modify the biologic makeup of people so that they are better able to ward off the potential carcinogenic impact of environmental substances. Classic examples of this approach are the development of vaccines such as that for influenza, measles, mumps, polio and many other acute infectious diseases. It is hoped that inevitably vaccines will be developed to prevent the causation of cancers in people even after they have been exposed to chemicals and other factors that are known to be carcinogenic. Other approaches include the identification of factors which predispose individuals to a very high-risk to the development of certain cancers. This may well lead into a more effective means for early detection and diagnosis of cancers so that available forms of treatment will be more effective. Finally in this regard, it is now well understood that most chemicals in their native state may by themselves be noncarcinogenic. In some fashion, the body transforms these chemicals into the active carcinogenic state. We have studies well underway to determine whether it is possible to enhance

various substances such as enzymes that may prevent this conversion from the inactive form to the active carcinogen. This seems to be possible in animal systems. To the extent that this is possible and feasible in man we may be able to live with our polluted environment to the extent that known carcinogens will not in fact produce cancer in people.

Finally, during the past 3 years or since the inception of the National Cancer Act of 1971, a number of very important new programs were expanded or begun in the area of environmental carcinogenesis. They are as follows:

(*a*) In general, and for the past 2 years, the National Cancer Institute has paid between 60 and 65 percent of all grants approved by study sections and by the National Cancer Advisory Board in environmental carcinogenesis.

(*b*) The NCI on its own initiative has established two chartered interagency committees among those agencies in the HEW as well as throughout the Federal Government that have an interest in or a regulatory responsibility for matters having to do with environmental carcinogenesis.

(*c*) Through the congressionally mandated International Cancer Research Data Bank, the Institute has established an effective system for storage and retrieval of reports from all over the world having to do with environmental carcinogenesis. Scientists from many countries can retrieve this information through data banks or through data systems at the National Library of Medicine, Bethesda, Md., through the World Health Organization in Geneva, through the International Union Against Cancer in Geneva and through various of our bilateral agreements such as that with the Soviet Union.

(*d*) The NCI has continued to support the International Agency for Research on Cancer in Lyon, France. This organization has been responsible through NCI support for the production of monographs having to do with all available information on known and suspected carcinogens from the environment.

(*e*) Through a contract with the Stanford Research Institute, Calif., we are better able to advise the lay public, academic, and commercial institutions as to the characteristics of certain environmental carcinogens. This may well provide us the best means yet for predicting the carcinogenic activity and impact on the American public.

(*f*) The NCI has continued to provide expert consultant positions to sister agencies whose activities have to do with environmental carcinogenesis. We also provide funds to those agencies who are already organized to more quickly implement research activities in this field.

(*g*) The National Cancer Advisory Board has established a special standing subcommittee chaired by Dr. Phillippe Shubik to advise the Director and his staff as to new opportunities in the overall field of environmental carcinogenesis.

(*h*) The NCI on its own initiative this year established a new program in in vitro carcinogenesis. This is a program that seeks to cooperate with other institutes of the NIH and other Federal agencies in an attempt to devise short-term and inexpensive

means to detect the deleterious (carcinogenic, mutagenic, teratogenic) potentials of chemicals to which man is exposed.

(*i*) During the past year (fiscal year 1974) a new program in nutrition was planned and is already being implemented to the extent of approximately an additional $1 million to $2 million. This program seeks to complement those projects already ongoing to determine whether certain food additives, or in general certain kinds of food stuffs, contribute to the induction or potentiation of various cancers in man (e.g. colon and rectal cancer). Projects are also designed within this program to determine whether certain forms of nutrition may aid the existing cancer patient during his treatment with radiotherapy and chemotherapy.

(*j*) Several weeks ago the NCI agreed to hold hearings on behalf of the FDA, among a peer group of experts from throughout the world, to assess new data regarding potential carcinogenic effects of cyclamates. This is essentially a new role for the NCI but is also an example of the Institute's continuing desire to use its expertise in an advisory capacity to the regulatory agencies.

Finally, Mr. Shriver, in answer to your specific question, to the extent that about 80 percent of man's cancers are extrinsically induced, approximately 80 percent of our total budget for research and treatment of environmentally caused cancers are attributable to these activities.

National Cancer Institute

Environmental Carcinogenesis
(Dollars in thousands)

	Actual FY 1974
Division of Cancer Research Resources and Centers	
Regular Grants	$15,971
Cancer Research Centers	10,801
Research Career Programs	303
Training Grants	2,584
Epidemiology	4,694
Construction	4,593
Subtotal, DCRRC	38,946
Division of Cancer Cause and Prevention	
Carcinogenesis	
In-House	4,063
Contracts	29,730
Frederick Cancer Research Center	(5,450)
Frederick Cancer Research Center Interagency Agreement	(996)
International Agency for Cancer Research (IARC)	(309)
Co-Carcinogenesis (Viral-Chemical)	
Contracts	2,400
Field Studies and Statistics	
In-House	1,182
Contracts	2,714
Lung Cancer Task Force	
In-House	396
Contracts	3,253
Smoking and Health - Contracts	5,976
Subtotal, DCCP	49,714
Division of Cancer Biology and Diagnosis	
In-House	40
Contracts	1,106
Subtotal, DCBD	1,146
Division of Cancer Control and Rehabilitation	
Contracts	3,273
Subtotal, DCCR	3,273
Office of the Director	
International Cancer Research Data Bank	284
Construction	1,175
NCI Management & NIH Management Fund	5,662
Subtotal, OD	7,121
Total, NCI Environmental Carcinogenesis	$100,200

Survival Rates

Mr. Shriver. You mention several times in your statement statistical improvements in survivability from various forms of cancer. However, in most cases you do not say what the time periods are during which these improvements have been accomplished. Are your statistics up to date enough so that you can tell this committee what progress has been made since the large expansion of your efforts began?

You might provide something for the record in regard to the relevance of your statistics on survivability in terms of if they are really current enough to be helpful in judging the effectiveness of this research.

Dr. Rauscher. I will provide for the record tables that summarize improvements in survival of cancer patients that have occurred for some forms of cancer over the period 1960–64 to 1970–71—for whites. In order to present the most up-to-date results, 1-year survival rates were used as a measure. Since the major expansion of the cancer program was initiated in 1972 following passage of the National Cancer Act of 1971, we are not able at this time to present survival data that reflect therapeutic policies instituted in 1972 or later.

[The material referred to follows:]

National Cancer Institute

survival rates

We compared survival of cases diagnosed in 1960–64 with cases diagnosed 1970–71. We defined "improved" survival as:

1. Three percentage points or more increase in survival and statistically significant at the 0.01 level, or

2. Ten percent or more improvement in possible increase in survival (for example, if 1960 survival was 80 percent, then a 20 percent increase is possible, as 10 percent of 20 percent equals 2 percentage points).

Using these rules cancers which accounted for more than 54 percent of all incident cases showed improvement. Table 1 shows these cancers, the percentage point improvement in 1-year survival (criterion 1, above), and the percent of possible improvement (criterion 2, above). This 54 percent is a minimum estimate, since we did not consider any of the cancers which individually made up less than 1 percent of all cancer incidence. (About 14 percent of all cancers fall into this "relatively rare" class.)

The leukemias and lymphomas are shown near the bottom of table 1 grouped together, since the improvement among them has been so dramatic. Childhood cancers are shown as a separate line with the data included where they belong in the site classification.

Mostly, survival and improvements in survival are correlated with the percent of patients definitively treated for their cancers. Increases in the proportion treated reflect "getting the message" out to physicians that treatment is really possible. For the sites we have examined, this proportion ranges from 98 percent for cancer of the uterine corpus (associated with 87-percent 1-year survival) to 33 percent treated for cancer of the pancreas (associated with 14-percent 1-year survival). Table 2 shows sites for which we did not report important improvement. Note that 7 out of 10 "no improvement" sites did show some improvement.

TABLE 1.—SITES/TYPES SHOWING IMPROVEMENT IN SURVIVAL 1960–71

Sites/type	1970–71 cases: 1 yr. survival	1970–71 cases: Percent treated	Increase in survival 1970–71 versus 1960–64	Percent of possible improvement	Percent of all incidence
Solid tumors:					
Breast (female)	90	97	2	16	13.9
Lung	29	79	4	5	13.1
Prostate	85	94	4	21	7.9
Bladder	79	95	5	19	4.6
Pancreas	14	33	4	4	3.1
Brain	47	89	8	13	1.6
Melanoma of the skin	87	97	3	19	1.5
Larynx	83	96	4	19	1.4
Leukemias and lymphomas:					
Chronic leukemia	68	56	7	18	1.4
Acute leukemia	36	88	15	19	1.2
Hodgkin's disease	82	95	9	33	1.1
Multiple myeloma	56	86	12	21	1.1
Lymphosarcoma	67	88	7	18	1.0
Reticulum cell sarcoma	46	94	11	17	.6
Total					53.5
Childhood (<15) cancer	70	97	15	33	1.2

TABLE 2.—SITES/TYPES NOT SHOWING (IMPORTANT) IMPROVEMENT IN SURVIVAL 1960–71

Sites/type	1970–71 cases: 1 yr survival	1970–71 cases: Percent treated	Increase in survival 1970–71 versus 1960–64	Percent of possible improvement	Percent of all incidence
Colon	65	89	0	0	10.4
Rectum	69	87	2	6.1	4.6
Corpus of uterus	87	98	0	0	3.8
Stomach	32	67	1	1.4	3.3
Cervix of uterus	82	96	1	5.3	2.7
Ovary	58	91	0	0	2.6
Kidney	62	89	3	7.3	1.8
Thyroid	87	96	1	7.1	1.3
Pharynx	61	95	3	7.1	1.0
Gall Bladder	24	57	2	2.6	1.0
Total					32.5

Mr. SHRIVER. Thank you.

Mr. FLOOD. Mr. Obey?

Mr. OBEY. Thank you, Mr. Chairman.

NCI ADVISORY COMMITTEE REPRESENTATION

Please provide the committee with a list of all individuals presently serving on NCI advisory committees, along with the organization with which they are affiliated, and any grant or contract which that organization has received from NCI since 1971.

Dr. RAUSCHER. I will provide that information for the committee.

NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

Mr. OBEY. Are you familiar with the National Center for Toxicological Research?

Mr. RAUSCHER. Yes; I am familiar with the National Center for Toxicological Research which is a bureau within the Food and Drug Administration. Members of my staff and I have met with Dr. Cranmer, Director, NCTR, to discuss the programs of our respective in-

stitutions to insure that such efforts are complementary and do not involve unnecessary program overlap. Further, Dr. Cranmer participated in a NCI-sponsored meeting of Federal agency heads concerned with chemical carcinogenesis which was held in August 1974. Also, the National Center for Toxicological Research is an active member of the Interagency Coordinating Committee consisting of 14 Federal agencies. This committee was established to provide coordination of the many interagency cancer-related research efforts and to alert member agencies to problem areas regarding environmental and occupational carcinogenesis.

Mr. OBEY. Do you know of any recent evaluations of that operation?

Dr. RAUSCHER. The only evaluation of the NCTR with which I am familiar is incorporated in the "Report of the NCI Ad Hoc Committee on Testing for Environmental Chemical Carcinogens," dated August 31, 1973.

Mr. OBEY. Could you tell the committee about the findings of any such evaluations?

Dr. RAUSCHER. I received the "Report of the NCI Ad Hoc Committee on Testing for Environmental Chemical Carcinogens" in September 1973. Following personal and staff review of the report, I assessed the document to be less than timely. The major recommendation of the report calls for the establishment of a Federal Council on Environmental Carcinogenic Hazards. I saw no reason to endorse this recommendation, as the Assistant Secretary for Health, DHEW, had already established a formal committee to coordinate toxicologic and related programs, including chemical carcinogenesis, and NCI had been invited to membership on that committee.

Further, the report recommends that an NCI unit should be charged with responsibility for identification of environmental carcinogens and formulation of appropriate recommendations. Such a unit, under the direction of the Scientific Coordinator for Environmental Carcinogenesis, NCI, was formed prior to receipt of the report.

More important, I was not, and am not, convinced the report accurately reflects the scientific and technical potential of the proposed NCTR effort to assess human carcinogenic hazards on the basis of laboratory animal studies. With full appreciation for the efforts of the NCI ad hoc committee, recent advances in biometric methodologies prompt me to the opinion that every effort must be made to test and validate procedures appropriate to quantitation of toxicologic and carcinogenic risks to man. For example, the Albert-Altshuler biometric procedure, proposed for trial by NCTR, would seem to have some potential to provide more rigorous, quantitative information as a basis for regulatory decisions for control of environmental toxicants and carcinogens.

In summary, the NCI ad hoc committee was charged to prepare a report on environmental chemical carcinogenesis for my office. It was my intention that the report in question would be advisory to my office. The report was received and was assessed to be less than timely. Consequently, I exercised what I considered my option and my responsibility by withholding endorsement of the report. Two copies of the report were provided for informational purposes to the Assistant Secretary for Health, DHEW, and the Director of NIH.

Mr. OBEY. Thank you.

Mr. FLOOD. Mr. Conte?

CANCER CONTROL

Mr. CONTE. Dr. Rauscher, you said that you were beginning to see results from your activities to promote the application of cancer knowledge in medical and health practice. Would you give us some examples of these results?

Dr. RAUSCHER. As you know, the cancer control program is only in its third year of operation. I think the most vivid example of results is the breast cancer detection projects. We have shown through the use of mammography, thermography and clinical examinations, that in 77 percent of women found to have breast cancer, the cancer has not spread to the axillary lymph nodes (of the armpit). This most favorable stage is seen only in 50 percent of patients whose disease is detected using less thorough methods.

Because the program is relatively new, some of the additional activities of the program cannot be measured at this time. However, by the end of fiscal year 1975, results of the cervical cytology screening program will begin to be compiled. Also, within the next 2 years, data will become available from: the Tyler, Tex., project involving detection in 850 workers exposed to asbestos; diethylstilbestrol exposed offspring; community hospital networks for treatment, rehabilitation and continuing care for acute leukemia in childhood lymphoma, breast cancer, head and neck cancer and others.

Mr. CONTE. You said that your cancer control program has become fully operational. Is that correct?

Dr. RAUSCHER. Yes. Fully operational, in that we have a Division of Cancer Control and Rehabilitation involved in projects covering all the intervention activities of: prevention; detection, diagnosis, and pretreatment evaluation; and treatment, rehabilitation, and continuing care. However, I remind you that we have only been operating for less than three years. Our activities to date are in the initial stages, but we have the structure for a comprehensive cancer control program.

Mr. CONTE. Does that mean that budget requests for cancer control should be stabilizing, or will they continue to increase?

Dr. RAUSCHER. Additional funding will be necessary for the cancer control program because there will continue to be new findings coming from research which must be translated into practice-ready techniques by the program and made available to the public and health professionals. Based on current projections, the budget for the cancer control program is expected to increase to 10 or 15 percent of the Institute's budget over the next 5 years.

INTERAGENCY COORDINATING COMMITTEE

Mr. CONTE. Dr. Rauscher, you mentioned the Interagency Coordinating Committee on Cancer. What are the 14 agencies involved?

Dr. RAUSCHER. The organizations which presently comprise the Interagency Coordinating Committee are:

Food and Drug Administration, National Center for Toxicological Research.

Center for Disease Control, National Institute for Occupational Safety and Health.

National Institutes of Health.

National Cancer Institute.

Health Resources Administration, National Center for Health Statistics.
Department of Agriculture.
National Science Foundation.
Department of Defense.
Veterans' Administration.
Energy Research and Development Administration.
Department of Labor.
Department of Transportation.
Environmental Protection Agency.
National Aeronautics and Space Administration.

Mr. CONTE. With 14 agencies involved in cancer-related work, is it really possible to eliminate duplication and overlap? How did so many groups get involved in cancer? When did this committee start work, and can you give us any examples of duplications that have been eliminated so far?

Dr. RAUSCHER. The fact that 14, and possibly more, agencies are involved in cancer-related work does not necessarily result in needless duplication and overlap; however, the need for effective coordination of program activities is clear. It should be noted that some agencies, such as the U.S. Department of Agriculture, Food and Drug Administration and the Department of Transportation, are involved by virtue of regulatory responsibility rather than responsibility for a basic, comprehensive cancer research program. Such agencies look to the National Cancer Institute for technical information and advice in support of regulatory actions. Other agencies, such as the National Center for Toxicological Research and the National Institute for Occupational Safety and Health, conduct basic research programs in areas such as development of test procedures for carcinogenesis bioassay and occupational-environmental carcinogenesis. Such programs are coordinated to insure complementation of effort and avoidance of unnecessary duplication of effort.

The rather large number of groups and agencies involved in cancer-related activities reflects the broad and diversified nature of the cancer problem and is properly indicative of the necessary and legal division of labor and responsibility required to insure Federal responsiveness to cancer problems in the areas of research, regulation, administration, treatment, and control.

The Interagency Coordinating Committee for the national cancer program was approved, as per regulations, by DHEW on December 11, 1974. However, it should be noted that the formal Interagency Committee in question was antedated by informal coordinating groups. One such group, the Interagency Collaborative Group on Environmental Carcinogenesis, was organized in January 1973. Another group was organized in August 1974 and involved agencies involved in chemical carcinogenesis (Center for Disease Control, Food and Drug Administration, Environmental Protection Agency, National Institute for Occupational Safety and Health, National Center for Toxicological Research, National Institute of Environmental Health Sciences and NCI).

The aforementioned groups and committees have served to provide for coordination of many interagency research efforts and, more specifically, have served to eliminate duplication of effort in areas such as

the biometry of risk quantitation, development of mutagenesis assay procedures as indicators of carcinogenesis, epidemiologic characterization of occupational and other groups at high-risk to cancer, geographic cancer clusters, and development of animal models for cancer research.

PARTICIPATION BY PRIVATE SECTOR

Mr. CONTE. What are you doing to achieve active participation by all components of the private sector? What are these components? Are you having any particular problems getting the private sector involved?

Dr. RAUSCHER. The organizations in the private sector performing cancer or cancer-related research are involved in the national cancer program in two major ways: (1) scientists representing private sector organizations have been and will continue to be involved in the major planning efforts supported by NCI, both for formulating and revising the national cancer program plan and also through participation in the planning of individual programs; (2) private sector organizations are involved by the very performance of cancer research and control of activities or through the support of these activities with private funds. There are two major types of private sector participation—the universities and medical schools which receive funds both from private sources and from the Federal Government, and those nonprofit organizations which receive no Federal funds but conduct their activities solely through private funds. We have not experienced any particular problems in involving the private sector in our planning activities or in establishing lines of communication for the exchange of research information.

CANCER SURVIVAL TRENDS

Mr. CONTE. Would you provide us with the 5-year survival statistics for the major cancers, compared to the survival rate several years ago?

Dr. RAUSCHER. In the attached table, survival trends are summarized for the nine leading cancer sites which account for 57 percent of all cancers in the end results series—51 percent in men and 63 percent in women. The trends cover three time periods from 1950 through 1969. Data for the 1940's have been excluded since it is difficult to determine if the improvement in survival was due to the introduction of antibiotics or to improved cancer therapy techniques. Also, 5-year survival results for the period 1970 to 1974 are not yet available. Included in the attached table are the percent diagnosed while localized and the percent of patients not definitively treated.

For cancer of the prostate there was an increase in the proportion of the cancers diagnosed while localized which was accompanied with improvement in the 5-year relative survival rate from 47 percent to 56 percent for all patients. Among the localized cases there also was an improvement from 61 to 68 percent.

Although there was no overall, all stage, improvement in survival for cancer of the lung, there was an improvement from 24 to 29 percent for men and 40 to 48 percent for women in the 5-year survival for localized cases; a small increase but nevertheless an increase.

For breast cancer, which accounts for almost a fourth of all cancers in women, there has been some improvement in 5-year survival—from 60 percent to 64 percent. For localized breast cases there was no improvement.

Survival has progressively increased for patients with melanoma of the skin and Hodgkin's disease although these occur much less frequently than the cancers in the table which I will include in the record.

[The information follows:]

Trends in Cancer Survival

Trends in Percent Localized, Percent Not Treated, 5-year Relative Survival Rates* for the Nine Leading Cancer Sites: 1950-1969

Site	Percent of All Cancers			Year of Diagnosis	Percent Localized		Percent not Treated		5-year Survival Rate All Stages		5-year Survival Rate Localized	
	M&F	M	F		M	F	M	F	M	F	M	F
Female Breast	11.8		23.8	1950-59	-	42	-	5	-	60	-	83
				1960-64	-	45	-	4	-	62	-	84
				1965-69	-	47	-	3	-	64	-	84
Lung and Bronchus	10.3	17.2	3.1	1950-59	18	19	39	42	7	11	24	40
				1960-64	19	19	27	28	8	12	27	42
				1965-69	18	17	25	22	8	12	29	48
Colon	8.0	7.1	9.1	1950-59	41	41	22	20	42	46	69	74
				1960-64	40	40	17	17	41	45	68	72
				1965-69	42	40	13	13	43	46	71	74
Prostate	6.3	12.4	-	1950-59	52	-	10		47	-	61	-
				1960-64	60	-	7		52	-	65	-
				1965-69	63	-	6		56	-	68	-
Rectum	5.2	5.7	4.8	1950-59	45	44	25	24	38	42	63	67
				1960-64	44	45	21	20	36	39	59	64
				1965-69	46	46	15	16	40	42	67	67
Cervix	4.8	-	9.8	1950-59	-	50	-	6	-	59	-	77
				1960-64	-	50	-	6	-	57	-	77
				1965-69	-	45	-	5	-	56	-	78
Stomach	4.5	5.7	3.4	1950-59	17	17	52	54	12	13	39	41
				1960-64	16	21	44	44	10	14	38	37
				1965-69	16	22	37	39	12	14	40	43
Corpus	3.5	-	7.0	1950-59	-	71	-	6	-	71	-	83
				1960-64	-	78	-	4	-	73	-	83
				1965-69	-	79	-	3	-	74	-	85
Pancreas	2.4	2.8	2.0	1950-59	14	13	74	76	1	2	3	6
				1960-64	15	17	77	80	1	2	7	3
				1965-69	12	11	74	84	1	2	5	4

*Source: 1950-59 End Results in Cancer Report No. 4
1960-69 Recent Trends in Survival of Cancer Patients, 1960-71

Mr. CONTE. The charge has often been made that increased cancer survival rates are the result of better surgical skills and technology, rather than cancer research per se. Do you have any information to support or refute such a contention.

Dr. RAUSCHER. Between 1900 and 1950, improved surgical technology did play a significant role in the cancer survival rate. But, since 1950, although surgical techniques have become more sophisticated, the improved survival rate was due largely to research advances. The reason that improved surgical technology will not substantially improve cancer survival rates is due to the realization that cancer is generally not localized when the patient has surgery. Therefore, it is not the surgery alone which allows survival, but the surgery combined with another mode of treatment.

LEADING CAUSES OF CANCER DEATHS

Mr. CONTE. What cancers are the leaders in cause of death, and could you provide a breakdown of the percentage of cancer-related deaths each type of cancer is responsible for? And would you also include the percentage of your research efforts which you might estimate as relating to each of these types of cancer?

Dr. RAUSCHER. In 1975, it is estimated that 365,000 cancer deaths will occur. Of that amount those with the highest mortality and percentage of total cancer deaths are: lung (22 percent), colon-rectum (13.5 percent), breast (9 percent), pancreas (5 percent), prostate (5 percent), leukemia (4 percent) and stomach (4 percent).

Because of the nature of cancer, it is somewhat difficult to define discrete resources to a particular type of cancer. A specific research finding may have application to more than one cancer site. Research into the environmental causes of cancer, as well as research into the viral causation of cancer cannot be specifically associated to any one particular cancer site. For example, environmental factors could bear on cancer in respiratory as well as digestive organs or urinary organs. Also, the Institute through its treatment research program screens many compounds which may have potential application to the clinician in the treatment of cancer. These costs may not be applicable to any one cancer site since they may have varied chemotherapeutic value. The Institute does have structured task forces for selected organ sites, that is, breast, lung, bladder, prostate, large bowel and pancreas. Resources have been identified specifically to these task forces and for 1975 their funding levels are: breast $9,475,000; lung $5,940,000; bladder $4,000,000; prostate $4,000,000; large bowel $4,000,000 and $300,000 for the newly created pancreas task force. As I previously noted, however, these discrete investments in site specific activities do not reflect a total investment in these types of cancers.

Generally, all cancer sites will benefit from the Institute's research efforts since these scientific advances will further the base of knowledge for all cancers. In this regard, the Institute in 1975 will devote 30 percent of the research portion of its resources to cause and prevention research, 9 percent to detection and diagnosis research, 40 percent to treatment research and 21 percent to cancer biology.

Mr. CONTE. What percentage of lung cancers might be attributed to smoking?

Dr. RAUSCHER. Of the estimated 91,000 new cases of lung cancer in 1975, the overwhelming majority will be observed among habitual cigarette smokers. A dose response relationship between the number of cigarettes smoked and incidence of lung cancer has been established beyond doubt by numerous epidemiological studies in men. The risk of developing lung cancer is approximately 13–15 per 100,000 in the nonsmoking population and nearly 150–200 per 100,000 among smokers, and it is estimated that 70 to 90 percent of new lung cancer cases are attributable to cigarette smoking.

Mr. CONTE. If smoking is a leading cause of cancer of the lungs, what are you doing to prevent smoking? How successful have you been?

Dr. RAUSCHER. Public education campaigns are being sponsored by the National Clearinghouse for Smoking and Health, now part of the Center for Disease Control, DHEW, the American Cancer Society, the American Heart Association, and other private organizations to promote public awareness of smoking hazards and to convince the smoker to quit.

The National Cancer Institute's cancer control program is partially sponsoring the activities of the National Clearinghouse for Smoking and Health. The Institute's smoking and health program also fosters the development of drugs that may be useful in reducing the smoking habit, and the development of behavioral smoke cessation techniques.

Public education efforts have had modest effects: today nearly 60 million Americans still smoke and evidence indicates that women and young people smoke at increasing rates. The reasons for the limited efficacy of education campaigns are mainly two: the very low budgets of the agencies involved and the pervading acceptance of traditional smoking habits in modern culture.

The development of drugs and behavioral smoking cessation techniques may attain a better measure of success, although their cost may effectively prevent their mass application in the smoking population.

Public education efforts have had a major indirect effect on the type of cigarettes marketed during the past 20 years, and a dramatic reduction in the amount of tar and nicotine yields of American commercial cigarettes has taken place. Recent epidemiological studies suggest that a smoker today must smoke more of modern cigarettes than he would have of cigarettes available 20 years ago, in order to develop the same risk of disease, and that smoking filter cigarettes for 10 years or more significantly decreases the risk of lung cancer as compared to smokers of unfiltered cigarettes.

Among other activities to reduce the risk of smokers, the National Cancer Institute's smoking and health program also promotes a reduction of cigarette toxicity as a measure of primary prevention. A comprehensive effort in the development of less hazardous cigarettes has identified several feasible approaches now being tested, and which should be ready for utilization in cigarette manufacturing during the next 2 to 5 years.

Mr. CONTE. Have there been any changes in the numbers of people smoking, or particularly the number of young people starting to smoke, over the past several years? What percentage of young people are starting to smoke?

Dr. RAUSCHER. The number of women smokers is increasing and lung cancer incidence among women is also increasing. However, women smoke less, and smoke more filter cigarettes than men do, and overall they show a lower incidence than men. The number of men smokers has remainded the same over the past couple of years.

In a study recently completed for the National Clearinghouse for Smoking and Health, the following statistics indicate an overall increase since 1970 in the percentage of young people smoking. During this period, the percentage of boys smoking has decreased, while smoking by girls has increased.

TEENAGE SMOKERS

Sex	Age	Percent of applicable population
1970:		
Boys	12–18	18.5
Girls	12–18	11.9
Total		30.4
1972:		
Boys	12–18	15.7
Girls	12–18	13.3
Total		29.0
1974:		
Boys	12–18	15.8
Girls	12–18	15.3
Total		31.1

Mr. CONTE. Why do you think that you have had so little success in treating the more common types of lung cancer? What makes them different from the ones in which you have made progress?

Dr. RAUSCHER. This is a very important question. One of the reasons is we have simply not identified a chemical compound which effectively kills large numbers of cancer cells in patients who have epidermoid carcinoma of the lung. The disease has often spread beyond the confines of the chest when first recognized. Therefore, surgery and radiotherapy cannot be used effectively. Our efforts in the clinic in this area are emphasizing the testing of completely new chemical compounds in such patients since the old drugs have been ineffective. It is not entirely clear why some tumors respond well to a given drug and others don't even within tumors originating from a similar organ. One interesting point in this regard should be made. It is recently become apparent that some patients with lung cancer have essentially a total collapse of their immunologic defenses shortly after the tumor is diagnosed. Even if patients have had surgery which apparently removes all the tumor their immunologic systems are badly compromised. It has been demonstrated that they lose killer-type lymphocytes, T cells, and this loss precedes the appearance of metastatic tumor by as much as 2½ to 3 months. Thus, there may be something unique to epidermoid carcinoma of the lung itself which

leads to a rapid compromise of the host's defenses. If so, we need to look at ways of building up the host in order to have him withstand both the onslaught of the tumor and the immunosuppressive effects of the drugs. This could be a form of immunotherapy and/or nutritional attempts at stabilizing the host, hyperalimenation—forced feeding the patient with a high caloric, high protein mixture intravenously. We are initiating studies in this very important area to go hand in hand with the therapeutic trials of new drugs.

CANCER BIOLOGY

Mr. CONTE. You stated that knowledge of the fundamental nature of cancer will come through research in cancer biology and molecular biology. How much work in, for example, molecular biology is being done outside of the Cancer Institute?

Dr. RAUSCHER. In 1975, the National Cancer Institute is supporting approximately $106 million in the area of cancer biology and molecular biology research. In addition to this amount, which is reflected as a separate item in our budget, the NCI also performs research in cancer biology which is more directly associated with the research thrusts of cause and prevention, detection and diagnosis, and treatment research. Other components of the National Institutes of Health also support approximately $200 million in research in the area of molecular biology research. These include National Heart and Lung Institute, National Institute of Allergy and Infectious Diseases, and the National Institute of General Medical Sciences. These research efforts pertain to metabolism, physiology, cell biology, biochemistry, virology, and immunology. Molecular biology research efforts are also conducted and/or supported by the Atomic Energy Commission, National Science Foundation, and Department of Agriculture as well as research sponsored at universities and by State and local governments.

NURSING AND REHABILITATION

Mr. CONTE. Would you tell me about your program in cancer nursing and rehabilitation? What are the approaches and problems in this field which make it different from other types of nursing and rehabilitation?

Dr. RAUSCHER. At the present time, the cancer control program is funding 11 projects in cancer centers, medical schools, and community hospitals which are structured to provide clinical experience with cancer patients in conjunction with classroom teaching for nurses. Also, an additional three projects will provide special training for nurses in enterostomal therapy.

The rehabilitation program of the Institute is a comprehensive effort encompassing three major areas: (1) restoration of physical functioning loss as a result of disease and/or treatment; (2) psychosocial support or counseling to enable the patient and family to cope with the emotional burdens of cancer diagnosis and treatment; and (3) restoration of the patient to the maximum vocational sufficiency as rapidly as possible after treatment. The demonstration of a comprehensive cancer rehabilitation program at major cancer centers and integrated cancer rehabilitation facilities at the community hospi-

tal level is the major thrust of this program. Also, projects for demonstrating that psychosocial counseling expedites rehabilitation are underway. Other activities include a project to modify employers' attitudes and practices toward workable cancer patients and the training and education of personnel both professional and vocational in cancer rehabilitation.

Many problems exist for both nurses and rehabilitation programs as they relate to cancer. Many of these problems stem from the nature of the disease whose disabling effects are compounded by the high probability that the disease will spread from the primary site to other areas of the body. Other problems also exist. For example, some treatment modalities currently in use may in some cases produce temporary effects more debilitating than the disease itself. Another factor which tends to make the nursing and rehabilitation required for cancer patients different from that required by patients with other diseases is the broad range of professional and technical expertise which is required to treat and rehabilitate the cancer patient. The expertise needed includes: surgeons, radiologists, nurses specializing in cancer care, counselors, psychologists, and physical therapists.

CANCER PREVENTION

Mr. CONTE. You stated the premise that in cancer, as in other diseases, prevention offers the best hope for ultimate control. How much of your budget are you devoting to cancer prevention?

Dr. RAUSCHER. Our budget includes $147,200,000 for cause and prevention research in fiscal year 1976. This is approximately 24 percent of our appropriation request of $605 million.

TESTING FOR CANCER-CAUSING AGENTS

Mr. CONTE. You referred to your program of testing potential cancer-causing agents. How does this program differ from the same sort of work done at the National Institute for Occupational Safety and Health (NIOSH)? Do you overlap, or do you complement each other, and how?

Dr. RAUSCHER. NIOSH's primary responsibility is the development and establishment of recommended occupational safety and health standards. Their research programs are directed toward developing criteria for new and improved job safety and health standards as opposed to determining whether or not a given chemical compound causes cancer. There is considerable collaboration between NIOSH and NCI which involves much discussion as well as exchange of ideas and proposals. The programs of these two organizations complement each other in terms of a common interest in identifying and examining potential carcinogens with the aim eventually to reduce and/or eliminate many of these compounds from the environment.

CANCER VIRUS PROGRAM

Mr. CONTE. Dr. Rauscher, the cancer-virus approach seems to be losing some credibility in the medical literature. The things I read indicate that probably very few cancers, and apparently not the most common ones, are concretely associated with viruses. Is this so, and if

it is, why is so much emphasis being placed on viral relationships to cancer?

Dr. RAUSCHER. It is a fact that many cancers in animals, including nonhuman primates, are caused by either RNA or DNA viruses. It is, therefore, only logical that some of man's cancers are also caused by viruses. Recently, human tumor cells from breast cancer, acute myelogenous leukemia, and other lymphoproliferative diseases were shown to contain viral components, proteins, nucleic acids, and indeed whole virus particles similar to those found to induce animal cancers. Laboratory studies show that many environmental chemicals induce the expression of tumor viruses which are capable of transforming cells to malignancy. Thus, viruses may be a major factor in chemical carcinogenesis.

Mr. CONTE. Couldn't a portion of the cancer-virus program be diverted to research on the environmental causes of cancer, which you seemed to consider important? How much of the National Institute for Environmental Health Sciences is devoted to cancer-related matters? Can you give any examples of cooperative efforts between your two institutes?

Dr. RAUSCHER. As stated above., the allocation of resources to the cancer-virus program was predicated on various factors. One aspect of the problem, which is well documented by laboratory studies, is the ability of viruses and chemicals to interact to produce cancer which would not occur by exposure to either of the agents individually. To increase the level of effort in environmental carcinogenesis at the expense of the cancer-virus program would be viewed as counterproductive at the present time. As more information becomes available regarding the importance of the viral background of an individual who may develop cancer as a consequence of the interaction of viruses with environmental chemicals, we will be better able to assess the extent to which viruses contribute to the morbidity and mortality of cancer in man.

The 1975 budget for NIEHS contains approximately $3,700,000 for cancer research. Included in this amount are funds for research dealing with the correlation between carcinogenic and mutagenic activity.

The major cooperative effort between NCI and NIEHS concerns the jointly funded project at Oak Ridge National Laboratory. This activity provides support for the Environmental Mutagen Information Center which collects, organizes, and disseminates information on chemical mutagens. Such activities provide an invaluable information source fundamental to the plannng and conduct of programs in environmetal mutagenesis/carcinogenesis.

Staff members from both Institutes have worked closely together in developing and conducting programs which seek to assess the predictive value of mutagenicity tests as prescreens for chemical carcinogens. It is anticipated that our two staffs will be working even more closely together in this area than they have in the past. Indeed, consideration is being given to the development of somewhat more formal arrangements if this would aid closer and more effective cooperation.

Current plans include a cost-sharing effort between our two Institutes in support of a symposium on asbestos-glass fiber carcinogenesis and a joint funding of a study on the carcinogenicity of ingested asbestos.

COMPREHENSIVE CANCER CENTERS

Mr. CONTE. Why isn't more emphasis being placed on national cancer centers in keeping with the 1971 National Cancer Act mandates? What is the cost per patient at the existing centers, and how does this compare to the cost of cancer treatment at other types of medical institutions?

Dr. RAUSCHER. At the present time, we have identified 17 comprehensive cancer centers as a part of the national cancer program. During fiscal year 1974, approximately $150 million was awarded at comprehensive centers through the peer review system by grants and contracts. This represented over 25 percent of the total NCI budget. In addition, NCI provided financial support to 63 specialized cancer centers. Before the end of this year, two, and perhaps three, more comprehensive cancer centers will be identified, extending further the nationwide accessibility of cancer expertise through effective demonstration and outreach programs. More than 106.5 million people currently live within 120 miles of a center. It will take as many as 30 to 31 such centers to get about 180 million Americans covered within 120 miles of a center. The total national cancer program (i.e. NCI and non-NCI) emphasis on comprehensive cancer centers is significant and is in keeping with the mandate in the National Cancer Act.

At the present time, we do not have specific data which will enable us to make quantitative comparisons of costs between various types of institutions. The cost of treatment per cancer patient was studied as part of the third national cancer survey. The cost study was limited to patient payments to hospitals, and excluded physicians fees and other charges not normally included as part of the hospital bill. This study determined that the average hospital cost per cancer patient over the 2-year study period was $2,289. The costs per disease site over that period varied from $956 for cancer of the cervix to $3,269 for stomach cancer. The detailed data from this study is available in the preliminary report, third national cancer survey, payment to hospitals, dated December 4, 1972. In addition, we are supporting an AACI project designed to permit assessment, design and evaluation of methods through which administrative information including hospital costs of member institutions can be derived and compared. The AACI is becoming a principal organization for coordination among the major cancer hospitals and research institutions in the country.

DETECTION AND PREVENTION OF PREVALENT CANCERS

Mr. CONTE. Why isn't more emphasis being placed on the detection and prevention of the more prevalent and treatment-resistant cancers (such as lung, colon, and pancreas), rather than the relatively infrequent cancers such as childhood leukemia, Hodgkin's disease, and lymphatic cancer? In other words, to what extent do you target your research toward the more prevalent cancers?

Dr. RAUSCHER. Considerable treatment research effort has been targeted to solid tumors including lung, colon and pancreas. A number

of new targeted clinical trials will be initiated with particular emphasis on breast, colon and ovarian tumors where new leads show great promise. Considerable emphasis is still placed on tumors with a lower incidence such as leukemia and Hodgkin's disease because the information gained in developing highly successful therapies for these diseases may provide important leads into the more prevalent and treatment-resistant cancers.

Our investment in research directly related to the common tumors is being steadily increased. For example, in the last 2 years we have more than doubled our prevention research program in lung cancer and tobacco. National organ site programs in breast cancer, large bowel, prostrate, bladder and recently, pancreas, have been established and are ongoing in order to accelerate the research in cause and prevention, detection and diagnosis, and treatment of these forms of cancer. This type of activity will continue to be expanded and diversified as the inputs from basic, developmental and applied research studies permit us to identify new opportunities for attacking the difficult problems posed by major tumors.

The extent to which research can be targeted to specific cancers depends upon the state of knowledge. Where there are few leads or ideas concerning approaches to specific cancers, we invest in basic studies of the cancer process. This is a vital activity since there are large gaps in our understanding of cancer processes and of effective ways of intervening against the major forms of cancer. At the next level we strive to identify ways in which basic research findings can be used as a basis for developing new materials and techniques which can be effectively directed to the prevention, detection or treatment of specific cancers. When this process leads to the development of demonstrably useful measures for detection and treatment, the use of these measures in medical practice is fostered through the cancer control program.

In cancer detection and diagnosis, for two of the top ten killers, breast—No. 3, and uterus—No. 8, the cancer control program actively promotes expanded efforts in breast cancer detection by X-ray mammography (ACS–NCI breast cancer detection demonstration units), and in the detection of cancer of the uterine cervix by the Pap test (with State health departments). Sizable research efforts are also in progress to develop new and improved mammographic methods with less radiation exposure, and to develop automated machines to help handle the vast load of Pap test cytologic specimens.

Significant applied research programs are in progress on the detection of lung cancer—No. 1 killer, bowel cancer—No. 2, and pancreas cancer—No. 4. The effort in lung cancer detection is a clinical test of sputum cytology for detection followed by flexible fiberoptic bronchoscopy for localization, and receives partial support from the cancer control program because of its expected early applicability in medical practice. The research effort to detect pancreas cancer is a small first step to generate new approaches by cooperative clinical study of the relative diagnostic value of existing methods. Additional efforts in applied research include the development of computer assisted X-ray equipment which should be helpful in diagnosing various types of cancer.

Behind these applied research efforts there are major basic research programs without identification with specific cancers, but which will lead sooner or later to better means of detection and diagnosis. Tumor immunology is one such discipline. We have great hopes that with the extremely sensitive and specific methods of the field, we shall be able to develop blood tests to detect cancers at an early stage. Finally the identification of causes and the formulation of preventive measures constitute a major program thrust. This budget includes nearly $150 million that will be spent on activities relating to cause and prevention. Such activities include major programs in chemical carcinogenesis and viral oncology. In the case of chemical carcinogenesis, NCI serves as a major performer in a sizable collaborative effort that is designed to identify and eventually remove or modify the substances (in the environment or workplace) that play a part in cancer causation.

In general the Institute strives to conduct a program that achieves a rational balance among the different approaches to cancer according to the opportunities for detection, treatment and prevention that appear to be ready for exploitation.

SCIENTIFIC MANPOWER

Mr. CONTE. During last year's hearings, you told me that there were possibilities of shortages in the academic disciplines from which cancer researchers are drawn. Does the same situation prevail today, or has anything changed during the past year? How do you propose to deal with this situation, if there is indeed a shortage?

Dr. RAUSCHER. To answer the first part of the question, we estimate that approximately 17,000 scientists are presently involved in the national cancer program (NCP). As analysis of total scientific manpower needed to support the full range of NCP research activities defined by the planning panels indicated that approximately 28,000, or an additional 11,000 scientists would be needed to support the NCP by 1982. Although the existing biomedical manpower pool is expected to provide some of these scientists, certain critical research areas still exist in which shortages can be expected to occur without further specialized cancer training. These areas are: carcinogenesis, epidemiology, radiation, viral oncology, immunology, drug development, chemotherapy, and tumor biology. The corresponding disciplines in which specialized training is required are as follows:

Research area	Disciplines
Carcinogenesis	Carcinogenesis.
Epidemiology	Epidemiology, biometry.
Radiation	Radiation oncology.
Viral oncology	Viral oncology, biochemical and biological virology.
Immunology	Immunology, immunotherapy.
Drug development	Molecular pharmacology.
Chemotherapy	Chemotherapy.
Tumor biology	Tumor and cell biology.

To answer the second part of the question, we hope to prevent shortages to the maximum possible extent through our training programs. If these programs prove to be inadequate and shortfalls do occur, specific critical needs will be identified at that time and efforts initiated to reverse the situation. It should be noted that once shortfalls occur, there is no quick or easy remedy. The leadtime required to train the

scientists is several years, during which time the corresponding research areas will suffer from the inability to follow promising leads and opportunities. The total impact of the National Research Service Award Act on the training program for the national cancer program is not known at this time. The National Academy of Sciences is conducting a study to define manpower needs for biomedical and behavioral research, as required by law. The results of this study will be used as a basis for developing NIH training programs. Initial results are due this summer for use in fiscal year 1976. We do not know at this time the extent to which these results will address the specific needs of individual categorical disease programs and the various research efforts conducted under these programs.

INTRAMURAL AND EXTRAMURAL RESEARCH

Mr. CONTE. How much of the research which you support is intramural, and how much extramural? Has this ratio been constant over the past several years, or is it changing? What are the relative advantages and disadvantages of intramural versus extramural research?

Dr. RAUSCHER. In 1975, approximately 12 percent of the Institute's available funds of $699,073,000 will be obligated in support of intramural research and 88 percent in support of extramural research. As the national cancer program has expanded, a greater percentage of the program is being supported by extramural research. For example, in fiscal year 1970, 20 percent of NCI funds were spent in support of intramural research as compared to 12 percent in 1975.

We do not think of intramural and extramural research in a context of one versus the other or in terms of advantages and disadvantages. Both support scientists of high caliber in the conduct of independent investigations in cancer and both are needed for the most effective pursuit of the objectives of the national cancer program. Extramural scientists, in addition to conducting research also provide a major portion of the teaching functions of universities and medical schools. Intramural scientists, in addition to conducting research, also serve as project officers on the hundreds of contracts funded by the NCI, and the intramural programs have historically produced many scientist-managers who assume leadership of major national programs.

FELLOWSHIPS AND TRAINING GRANTS

Mr. CONTE. It seems that you are making significant reductions in fellowships and training grants. How do you foresee this affecting the work of the Institute? Now and in future years? What is the rationale for this cutback?

Dr. RAUSCHER. The Institute's fellowships and training programs are in a state of transition which will extend through 1976. Both the old fellowships program and the old training grants program will continue to be phased out in 1976. The phaseout of these two programs are reflected in the Institute's budget as a $7,360,000 decrease from 1975 to 1976. However, the new National Research Service awards program, designed to replace the old programs, will increase $3,360,000 in 1976 over 1975.

RESEARCH GRANT PROGRAM

Mr. CONTE. Your justification indicates that the funds for noncompeting grants will not permit the funding of all noncompeting awards, but only those of the highest priority. What percent of noncompeting grants will you not be funding this year? What does this do to ongoing research efforts? Will teams and laboratories melt away unfunded?

Dr. RAUSCHER. In the regular research grant program 398 grants totaling $23.9 million would not be funded and this amounts to 26.7 percent of the total number of noncompeting continuation grants in the program. The total number and amount of all noncompeting research grants for NCI which will not be funded is 485 grants and $53.5 million. This total reduction includes $23.9 million of regular research grants, $23.8 million of cancer center grants, and $5.8 million in other research programs of large bowel, bladder, prostate and pancreas task force; clinical education; and radiation development.

Unless these investigators can find alternative sources of funds to continue their research, postponement and/or abandonment of ongoing research efforts will occur.

As Dr. Cooper, Acting Assistant Secretary for Health, mentioned in his opening statement before this committee, the budget submitted to you by the President in early February was prepared on the assumption that the proposed rescissions for health programs would be approved by Congress. Since these rescissions were rejected, we will obligate the funds this year, and the awarding of additional grants in 1975 will generate increased continuation requirements in 1976.

We will have to review our grant programs on a project-by-project basis to determine how best to fund our programs. The budget justification does not reflect final decisions as to the distribution of new and continuation projects for the total funds requested in the budget.

Mr. CONTE. Would you explain exactly what you mean by competing and noncompeting grants and fellowships? What types of things would fall into each category, and why is it necessary to have both?

Dr. RAUSCHER. Grant applicants currently request from 1 to 5 years of support for their proposed research and fellowships are limited to 3 years maximum. The average project period for those recommended and funded is 3 years for research and 2 to 3 years for fellowships. When the first year is funded a moral commitment results to fund the remaining years of the project. Thus, to receive support for the first year of a project period an applicant must successfully compete for funds, which must be approved by the National Cancer Advisory Board, with a good priority score. The remaining committed years are noncompeting continuation years. At the end of the project period the grantee must submit a competing renewal application if he wishes to receive continued support for his research. New applications and competing renewal applications compete for funds, and are called competing. Noncompeting grants and fellowships are, therefore, continuations.

The grant cycle for a successful grantee for research might go as follows: First year, competing application; second year, noncompeting continuation grant; third year, noncompeting continuation grant; fourth year, competing renewal; fifth year, noncompeting continuation, et cetera.

CAUSE AND PREVENTION RESEARCH

Mr. CONTE. Dr. Rauscher, in your justification it indicates that there will be a reduction of four positions and about $17 million in cancer cause and prevention research. I think that cancer prevention should be a top priority item; couldn't cuts be made from other portions of the cancer program?

Dr. RAUSCHER. At the $605 million level, all program activities sustain a decrease—cause and prevention research approximately 10 percent and treatment research approximately 12.5 percent. The relative priorities between the various research components of the program are based on the scientific judgment of the research that can be effectively pursued at this time, while attempting to maintain an overall program balance in the wide spectrum of activities that must be pursued.

BASIC RESEARCH

Mr. CONTE. Dr. Rauscher, do you honestly feel that sufficient basic research has been completed to justify such a dedication of resources to specific cancer research?

Dr. RAUSCHER. There are two major approaches to the control of disease: the development of techniques for prevention and treatment based on the full understanding of the biological phenomena underlying the disease, and the development of safe and effective techniques for prevention and treatment based on sufficient—although not full—understanding of the underlying biological phenomena. The history of disease control reflects both approaches. Our general approach has been that when the results of basic research provide an information base in a particular area of cancer research which is judged to be mature enough to warrant a specific program effort, then we develop a program in this area. Furthermore, the NCI has felt that since five or six organ sites account for approximately 80 to 85 percent of all cancer deaths, then specific efforts are justified in these areas, efforts which range from basic research to the applied aspects of cancer control.

RESEARCH TRAINING GRANTS

Mr. CONTE. How many research training grants will you be able to fund with this budget? How does that compare to last year?

Dr. RAUSCHER. In 1976, the Institute will be able to award 901 fellowships and 47 training grants. For 1975, 831 fellowships and 109 training grants will be funded.

CURE-ORIENTED RESEARCH

Mr. CONTE. Dr. Rauscher, despite the fact that many leads concerning prevention of cancer that are related to environmental origins have lately emerged, it seems that you are devoting the overwhelming proportion of funds for cures. What portion of your support is for cures, and what part for prevention? Do you foresee any change in that in the near future?

Dr. RAUSCHER. Currently, approximately 32 percent of the total NCI budget is committed to treatment research, and approximately 24 percent of the budget is committed to cause and prevention re-

search. The relative size of these efforts is based on the scientific judgment of NCI and its advisers as to the opportunities and leads which can be effectively pursued at this time. Since cause and prevention research is characteristically longer term than treatment research, usually the results of treatment research can provide more direct benefits to the patient in the short term. For the near future, I see the relative proportions of these two research areas remaining approximately the same. However, assessment of research opportunities is a continuing process, and program changes are made based on these assessments.

Mr. CONTE. Dr. Rauscher, of the members of the President's Cancer Panel and the National Advisory Board, do any have a background in such things as epidemiology, preventive medicine, or related preventive fields? Or might they all be described as "cure-oriented"?

Dr. RAUSCHER. Several members of the National Cancer Advisory Board and the President's Cancer Panel have backgrounds in preventive medicine and related fields, and are presently active in these areas. The members and their specialities will be supplied for the record:

	Degree	Speciality
National Cancer Advisory Board:		
Harold Amos	Ph.D	Bacteriology.
William O. Baker	Ph. D	Physical chemistry.
Frank J. Dixon	M.D	Experimental immunology; pathology.
Werner Henle	M.D	Virology, immunology.
Phillippe Shubik	Ph.D. (D.M.-Oxford)	Environmental and industrial carcinogenesis; pathology; oncology.
Howard E. Skipper	Ph.D	Biochemistry.
President's Cancer Panel:		
Ray D. Owen	Ph.D	Genetics, immunology.

Mr. CONTE. Thank you.

Mr. FLOOD. Thank you, Dr. Rauscher.

Dr. RAUSCHER. Thank you, Mr. Chairman.

JUSTIFICATION OF THE BUDGET ESTIMATES

Appropriation Estimate

NATIONAL CANCER INSTITUTE

For carrying out, to the extent not otherwise provided, title IV, parts A and 1, of the Public Health Service Act with respect to cancer, [$691,666,000] $605,000,000.

For the "National Cancer Institute" for the period of July 1, 1976, through September 30, 1976, $151,250,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation[1/]

	1975 Estimate	1976
Appropriation	$691,666,000	$605,000,000
Comparative transfers to:		
"Office of the Director" (For Department-wide reductions in public affairs)	-55,000	---
"Research Resources, NIH" (For Rhesus Monkey Supply Program)	-172,000	---
"Office of the Director" (For transfer of Institutional Relations Branch from Division of Research Grants)	-78,000	---
Subtotal, budget authority	691,361,000	605,000,000
Unobligated balance, start of year	7,712,000	---
Total, obligations	$699,073,000	$605,000,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 estimate - $100,000; 1976 - $100,000.

Summary of Changes

1975 Estimated obligations	$699,073,000
1976 Estimated obligations	605,000,000
Net change	-94,073,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1974 pay increase	---	---	---	*+$734,000
2. Within-grade pay increases	---	---	---	+586,000
3. Wage-board pay increases	---	---	---	+65,000
4. Extra day of pay	---	---	---	+151,000
5. Bureau of Employees Compensation	---	---	---	+13,000
6. FTS rate increase	---	---	---	+65,000
7. Service and Supply Fund	---	---	---	+23,000
8. Payment to NIH Management Fund	---	19,148,000	---	+1,609,000
Subtotal	---	19,148,000	---	+3,246,000
B. Program:				
1. Research grants				
a. Non-competing continuations - regular program	---	75,555,000	---	+54,020,000
b. Competing (new, continuations, and supplementals)	---	59,585,000	---	+34,725,000
2. Fellowships				
a. Non-competing continuations	---	1,829,000	---	+6,760,000
b. Competing (new, continuations, and supplementals)	---	10,237,000	---	+5,198,000
3. Intramural laboratory and clinical research	512	19,250,000	-7	+1,907,000
4. Collaborative research and support	909	38,466,000	-27	+3,099,000
5. Research management and program services	435	29,888,000	-27	+3,661,000
Subtotal	1,856	234,810,000	-61	+109,370,000
Total, increases				+112,616,000

Summary of Changes--continued

	1975 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Decreases:				
A. Program:				
1. Research grants				
a. Non-competing completed or converted to competing status.....	---	---	---	-$49,701,000
b. Competing completed or converted to non-competing.....	---	---	---	-59,585,000
c. Special programs.....	---	$139,459,000	---	-22,257,000
2. Fellowships				
a. Non-competing completed or converted to competing status.....	---	---	---	-792,000
b. Competing completed or converted to non-competing.....	---	---	---	-10,237,000
3. Training grants				
a. Non-competing completed or converted to competing status.....	---	10,097,000	---	-4,929,000
4. Research and development contracts.....	---	200,174,000	---	-31,327,000
5. Construction.....	---	45,010,000	---	-23,010,000
6. Cancer control.....	50	50,375,000	-9	-4,851,000
Total, decreases.....			-9	-206,689,000
Total, net change.....	---	---	-70	-94,073,000

Explanation of Changes

Increases:

A. Built-in:--These increases will provide: $734,000 for annualization of 1974 pay increases; $586,000 for within-grade increases; $65,000 for wage-board pay increases; $151,000 for an extra day of pay; $13,000 for increased contribution to the Bureau of Employees Compensation; $65,000 for increased costs for use of the Federal Telecommunications System; $23,000 for increased costs to the Service and Supply Fund and $1,609,000 for increased support to the NIH Management Fund. The following reflects the distribution of built-in increases as they relate to the program activities:

Explanation of Changes--continued

Program Activity	Annualization of 1974 pay increase	Within-grade pay increases	Wage-board pay increases	Extra day of pay
Cause and Prevention Research	$191,000	$153,000	$17,000	$39,000
Detection and Diagnosis Research	125,000	100,000	11,000	26,000
Treatment Research	272,000	217,000	24,000	56,000
Cancer Biology	127,000	101,000	10,000	26,000
Cancer Centers Support	1,000	1,000	1,000	---
Research Manpower Development	1,000	---	---	1,000
Construction	1,000	1,000	1,000	---
Cancer Control	16,000	13,000	1,000	3,000
Total Built-in	734,000	586,000	65,000	151,000

Program Activity	Bureau of Employees Compensation	FTS Rate Increase	Service and Supply Fund	NIH Management Fund
Cause and Prevention Research	$3,000	$18,000	$6,000	$26,000
Detection and Diagnosis Research	2,000	11,000	4,000	271,000
Treatment Research	5,000	24,000	9,000	1,129,000
Cancer Biology	2,000	11,000	4,000	76,000
Cancer Centers Support	---	---	---	46,000
Research Manpower Development	---	---	---	6,000
Construction	---	---	---	47,000
Cancer Control	1,000	1,000	---	8,000
Total Built-in	13,000	65,000	23,000	1,609,000

B. Program:

1. Research grants

a. The increase of $54,020,000 in non-competing regular research grants represents the increased costs for continuation in 1976 of competing continuations and new research grants funded in 1975. The increase is reflected by the program activity structure as follows: Cause and Prevention Research - $8,378,000; Detection and Diagnosis Research - $4,916,000; Treatment Research - $11,371,000; and Cancer Biology - $29,355,000. However, the funds for non-competing grants will not permit the funding of all non-competing awards, but only those of the highest priority.

b. The increase of $34,725,000 in competing research grants reflects: (a) $15,909,000 for 266 new awards; (b) $15,323,000 for 196 competing continuations; and (c) $3,493,000 in supplementals. The increase is reflected by the program activity structure as follows: Cause and Prevention Research - $2,209,000; Detection and Diagnosis Research - $750,000; Treatment Research - $14,392,000; and Cancer Biology - $17,374,000.

Explanation of Changes--continued

2. Fellowships

a. The amount of $6,760,000 in non-competing fellowships represents an increase over the 1975 non-competing level for the 1976 cost of continuing previously awarded competing and non-competing fellowships in 1975. Total non-competing fellowships will increase by 381 over the 160 in 1975. Funding for the Fellowships Program is included in the Research Manpower Development Program Activity.

b. The amount of $5,198,000 in competing fellowships represents the level of support for 360 fellowship awards in 1976.

3. Intramural laboratory and clinical research--The program increase of $1,907,000 will allow for modest increases for research efforts in the detection and diagnosis ($727,000) and treatment ($325,000) of cancer and cancer biology ($855,000).

4. Collaborative research and support - The program increase of $3,099,000 will permit a modest expansion of in-house research efforts and contract management in the areas of cause and prevention ($1,253,000); treatment research ($1,690,000); and detection and diagnosis ($156,000).

5. Research management and program services--The program increase of $3,661,000 will provide resources to support the activities of the Institute called for by the National Cancer Act. Increases in this area will include support for: the overall administration and guidance to the National Cancer Program; expanded international research activities including an International Cancer Research Data Bank; further updating and refinement of the National Cancer Program Plan; and increased support for the management and administration of both research contracts and grants. The following is the distribution of increases for research management and program services by program activity structure.

Program Activity	Amount
Cause and Prevention Research	$343,000
Detection and Diagnosis Research	868,000
Treatment Research	1,320,000
Cancer Biology	1,015,000
Cancer Centers Support	45,000
Research Manpower Development	14,000
Construction	45,000
Cancer Control	11,000
Total, increases	$3,661,000

Decreases:

A. Program:

1. Research grants

a. The decrease of $49,701,000 represents 1,759 non-competing regular research grants that were completed in 1975 or that are being converted to competing status in 1976. The decrease is reflected by the program activity structure as follows: Cause and Prevention Research - $7,708,000; Detection and Diagnosis Research - $4,523,000; Treatment Research - $10,462,000; and Cancer Biology - $27,008,000.

Explanation of Changes--continued

b. The decrease of $59,585,000 represents the completion or conversion to non-competing status of 737 competing grants. The decrease is reflected by the program activity structure as follows: Cause and Prevention Research - $6,919,000; Detection and Diagnosis Research - $1,287,000; Treatment Research - $29,571,000 and Cancer Biology - $21,808,000.

c. The decrease of $22,257,000 represents a decrease of $15,135,000 in the Cancer Research Centers Program; a decrease of $3,050,000 for grant task force programs, a decrease of $2,072,000 in the Clinical Education Program; and a decrease of $2,000,000 in the Radiation Development Program. The decrease for the Cancer Research Centers Program is reflected by the program activity structure as follows: Cause and Prevention Research - $510,000; Detection and Diagnosis Research - $2,135,000; Treatment Research - $2,778,000; Cancer Biology - $4,637,000; and Cancer Centers Support - $5,075,000. The decrease for the grants task force programs is reflected by the program activity structure as follows: Cause and Prevention Research - $991,000; Detection and Diagnosis Research - $1,101,000; and Treatment Research - $958,000. The decrease for the Clinical Education Program is reflected under the Program Activity Structure of Research Manpower Development. The decrease for the Radiation Development Program is reflected under Treatment Research in the Program Activity Structure.

2. Fellowships

a. The decrease of $792,000 represents the completion of 90 fellowships.

b. The decrease of $10,237,000 represents the completion or conversion to non-competing status of 671 competing grants.

3. Training grants--The decrease of $4,929,000 represents the completion of training grants in accordance with the phase-out of this program when training under previously approved training grants is completed.

4. Research and development contracts --The program decrease of $31,327,000 will permit continued efforts in the search for viruses which cause cancer in man; continued research in the modalities of cancer therapy particularly combined modalities; research in the carcinogenic potential of selected chemicals; investigation in the role of immunology in cancer research. The decrease in Research and Development Contracts is reflected by the program activity structure as follows: Cause and Prevention Research - $11,403,000; Detection and Diagnosis Research - $6,156,000; Treatment Research - $12,665,000; and Cancer Biology - $1,103,000.

5. Construction--The decrease of $23,010,000 will still allow resources for new construction as well as the modernization and renovation of existing space for cancer laboratory and clinical research purposes.

6. Cancer Control--The program decrease of $4,851,000 will reduce the on-going activities of the Institute's Cancer Control Program including the 27 centers established for the early detection of breast cancer, as well as other efforts in the prevention, screening, diagnosis, treatment, rehabilitation, and education related to cancer research.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
25	Research						
26	(a) Cause and Prevention Research.....	581	$164,095,000	577	$147,200,000	-4	-$16,895,000
29	(b) Detection and Diagnosis Research	272	54,225,000	264	46,990,000	-8	-7,235,000
32	(c) Treatment Research..	567	223,000,000	529	195,400,000	-38	-27,600,000
35	(d) Cancer Biology.....	389	106,000,000	385	102,400,000	-4	-3,600,000
37	Resource Development						
38	(a) Cancer Centers Support.....	16	27,222,000	14	22,241,000	-2	-4,981,000
39	(b) Research Manpower Development.....	10	27,602,000	8	21,552,000	-2	-6,050,000
41	(c) Construction.....	12	45,552,000	10	22,637,000	-2	-22,915,000
42	Cancer Control (a) Cancer Control.....	59	51,377,000	49	46,580,000	-10	-4,797,000
	Total obligations.....	1,906	699,073,000	1,836	605,000,000	-70	-94,073,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	1,906	1,836	-70
Full-time equivalent of all other positions	248	263	+15
Average number of all employees	2,071	2,081	+10
Personnel compensation:			
Permanent positions	$33,453,000	$34,884,000	+$1,431,000
Positions other than permanent	2,631,000	2,786,000	+155,000
Other personnel compensation	945,000	1,020,000	+75,000
Subtotal, personnel compensation	37,029,000	38,690,000	+1,661,000
Personnel benefits	5,069,000	5,208,000	+139,000
Travel and transportation of persons	2,900,000	3,419,000	+519,000
Transportation of things	235,000	250,000	+15,000
Rent, communications and utilities	1,670,000	1,700,000	+30,000
Printing and reproduction	1,170,000	1,210,000	+40,000
Other services:			
Project contracts	259,459,000	213,005,000	-46,454,000
Payment to NIH Management Fund	19,148,000	20,757,000	+1,609,000
Other	23,661,000	30,497,000	+6,836,000
Supplies and materials	13,700,000	14,900,000	+1,200,000
Equipment	3,870,000	3,900,000	+30,000
Grants, subsidies and contributions	331,162,000	271,464,000	-59,698,000
Total obligations by object	699,073,000	605,000,000	-94,073,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1975 House Report	
Comprehensive Cancer Centers	
1. The Committee recognizes the importance of the Centers program. Additional funds will allow the National Cancer Program to provide core support and research funds for new and existing centers (page 24).	1. Currently, the NCI has recognized 17 Comprehensive Cancer Centers. This includes three Comprehensive Centers that were identified before the National Cancer Act of 1971 was passed. As a result of the continued growth and improvement in Cancer Centers during the past year, over half of the country's population now has access by means of surface transportation to and from a major multidisciplinary center. In a period of one day, those patients referred to these centers can receive consultation or special treatment as outpatients.

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1975 Senate Report	
Pap Test and Breast Cancer Detection	
1. The Committee was very pleased with the progress for Pap testing and Breast Cancer detection and treatment programs, but urged increased efforts in both areas (page 40).	1. In cooperation with State and Territorial Health Departments, 24 projects were supported in the cervical cancer screening program. It is estimated that by the end of FY 1975, 500,000 women will have been screened in this program. This program is aimed at high-risk women who have never had a Pap test or who are infrequent recipients of cervical cancer screening. The Division of Cancer Control and Rehabilitation now includes 27 demonstration projects, co-funded with the American Cancer Society for early detection of breast cancer. These projects will screen 270,000 women annually for breast cancer.
Cancer Control - Psychosocial Support	
2. The Committee directs that NCI include within its clinical education trial program, programs relating to psychosocial support and to encourage through this program the training of students in medical and nursing schools to deal with terminally ill patients and their own reactions to the terminally ill patients (page 40).	2. NCI is developing a wide range of program activities in rehabilitation research, psychosocial rehabilitation, and comprehensive services and techniques, such as vocational rehabilitation and physical restoration. Some of the projects in this area demonstrate patient rehabilitation service systems that provide medical, psychosocial, and social support to the cancer patient.
Cancer Immunology	
3. The Committee was very interested in Cancer immunology and the use of highly sensitive immunologic reactions to detect cancer cells or their products and directed the NCI to move ahead rapidly in this area (page 41).	3. Evidence for an immune response to tumors is steadily increasing. Immune responses to antigens on tumor cells have been unequivocally demonstrated in animal model systems, and there is evidence that humans respond to antigens specific to their tumors. It is expected that this area will be emphasized heavily in the future.

Item	Action taken or to be taken
1975 Senate Report	
Human Cancer Virus	
4. The Committee felt that the efforts to identify and isolate a human cancer virus must continue during FY 1975 (page 41).	4. The isolation of a candidate human leukemia virus from a patient with acute myelocytic leukemia was reported recently. This may be the first successful isolation of a human cancer virus, and should open the way for new approaches to research on detection, diagnosis and treatment of human cancer. For example, work on the unique proteins of the virus itself or proteins it may induce on the surface of the leukemic cell may result in new markers to diagnose the disease or monitor the effectiveness of drug treatment.
Nutrition and Cancer	
5. The Committee also notes that the National Cancer Act Amendments of 1974 requires NCI to gather and disseminate information on the relationship between nutrition and cancer and the role of nutrition in the treatment of cancer patients (page 42).	5. Plans are under way to study the role of nutrition in the causation of cancer, such as caloric intake, diet composition, diet deficiencies, alcoholism, food preservation and preparation, as well as to study the problem of competition for available nutrients between the host cells and the tumor cells. New information materials about nutrition and cancer are in press and will be made widely available to patients and their families. Two planning conferences are scheduled for spring, 1975, in the causation and therapy aspects of nutrition.
Manpower Development	
6. The Committee anticipates that the vital area of manpower development will be significantly expanded as a result of the increased funding level provided by the Congress (page 42).	6. During 1975, the NCI awarded 831 fellowships and 109 graduate and clinical training grants. Through these mechanisms, which include the newly instituted National Research Service Award Program, the NCI will support scientists in eight major research areas: carcinogenesis, epidemiology, radiation, viral oncology, immunology, drug development, chemotherapy, and tumor biology.

Item	Action taken or to be taken
1975 Senate Report	
Construction	
7. The Committee directs that $4,300,000 of the increase of construction funds be used to complete construction at the Children's Cancer Research Foundation in Boston, Massachusetts (page 42).	7. In November, 1974, the National Cancer Advisory Board recommended approval and funding of $4,896,863 to the Children's Cancer Research Foundation in Boston, Massachusetts. These funds will complete five floors of shell space, that were constructed with the assistance of a 1972 award of $6,000,000 from the NCI. The additional funds will be awarded in FY 1975.

Authorizing Legislation

Legislation	1976 Authorized	1976 Appropriation requested
Public Health Service Act:		
Section 301 - Research and Investigation.....		
Title IV, Part A -- National Cancer Institute.....	$898,500,000	$586,837,000
Section 409 (b) -- Cancer Control.....	(68,500,000)	
Section 410C. -- Research.....	(830,000,000)	
Title IV, Part I -- National Research Service Awards.....	1/	18,163,000 2/

1/ Authorization expires June 30, 1975: extension legislation is proposed.

2/ Funding estimate only. Total appropriation requested for this Institute is $605,000,000.

National Cancer Institute

(Comparable)

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$148,709,000	$152,359,000	$158,074,000	$158,609,000
1967	158,581,000	164,863,000	169,863,000	169,863,000
1968	176,246,000	176,246,000	183,941,000	176,225,000
1969	180,869,000	175,754,000	184,754,000	178,311,500
1970	173,887,000	173,887,000	191,703,000	183,648,063
1971	197,404,000	220,651,000	228,651,000	223,651,000
1972	369,063,000	371,479,000	391,469,000	372,881,000
1973	427,335,000	485,418,000	485,418,000	485,418,000 1/
1974	499,913,000	522,296,000	579,913,000	527,399,000 2/
1975	599,695,000	659,695,000	754,695,000	691,361,000
1976	605,000,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

National Cancer Institute

(Actual)

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966[1]	$153,968,000	$157,618,000	$163,768,000	$163,768,000
1967	163,957,000	170,656,000	175,656,000	175,656,000
1968	183,356,000	183,356,000	192,356,000	183,356,000
1969	187,707,000	182,592,000	191,592,000	185,149,500
1970	180,725,000	180,725,000	200,000,000	190,486,100
1971	202,383,000	227,383,000	235,383,000	233,160,000
1972	334,338,000	337,531,000	358,233,000	378,794,000
1973	432,205,000	492,205,000	492,205,000	492,205,000
1974	500,000,000	522,383,000	580,000,000	527,486,000[2]
1975	600,000,000	479,506,000[3]	755,000,000	691,666,000
1976	605,000,000			

1/ Includes $10,000,000 transferred from "Special Cancer Research" appropriation in 1966.

2/ Appropriation after reduction.

3/ Excludes contracts not considered by House due to lack of authorization.

Justification

National Cancer Institute

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	1,906	$42,098,000	1,836	$43,898,000	-70	+$1,800,000
Other expenses.....	---	656,975,000	---	561,102,000	---	-95,873,000
Total.....	1,906	699,073,000	1,836	605,000,000	-70	-94,073,000

General Statement

The National Cancer Act of 1971 established the National Cancer Program (NCP) to conduct a nationally coordinated effort to achieve progressive reductions in the incidence, morbidity, and mortality of cancer leading to the eventual control of the disease. Achieving this goal is a long-term effort; therefore, the strategy of this program is to provide for a balanced program covering the entire spectrum of research, from basic through applied and developmental, by the implementation of laboratory, field and clinical programs that are judged most likely to produce the information and needed technology that can be transferred to medical practice in preventing and treating cancer.

The National Cancer Program Strategic Plan, prepared in 1973, was the first major output of the continuous planning process being carried out within the NCP. Over 400 of the leading cancer experts in the United States have participated in the development of the initial Strategic Plan together with the other plans which comprise the National Cancer Program Plan (NCPP). A recent revision to the NCP Science Strategy identifies three major components of the NCP - Research, Cancer Control and Resource Development. Research and Cancer Control together, are the major scientific components of the NCP. The Research objectives are organized in terms of the four major research thrusts: cause and prevention research; detection and diagnosis research; treatment research; and cancer biology. The Cancer Control objectives have been organized in terms of major intervention areas: prevention; detection, diagnosis and pretreatment evaluation; and treatment, rehabilitation and continuing care. A wide range of activities are conducted which support the implementation of the scientific research and control efforts. These efforts include programs for resource development (core support of cancer centers, exploratory projects, manpower development, and construction) and supporting activities such as the International Cancer Research Data Bank, establishment of an Interagency Coordinating Committee, International Affairs and Communications.

Cause and prevention research has four major objectives which are to develop the means: (1) to reduce the effectiveness of external agents for producing cancer; (2) to modify body mechanisms so as to minimize the hazards of cancer-inducing agents; (3) to prevent transformation of normal cells to cells capable of forming cancers; and (4) to prevent progression of precancerous cells to cancers, the development of cancers from precancerous conditions and the spread of cancers from primary sites. A major portion of the resources committed to cause and prevention research is utilized on projects designed for reducing the effectiveness of external agents for producing cancer. Cause and prevention research is also concerned with the identification of high-risk groups for various cancers, studies

marking the progression of a normal cell to the cancerous state, and studies leading to a means to interrupt the cancerous process or identification of factors capable of inhibiting the carcinogenic process. Extensive research and consultation has been undertaken in the field of environmental carcinogenesis and the problems of evaluation of risk in environmental carcinogenesis have been documented.

Research during the past year has uncovered new evidence regarding the carcinogenic factors attributable to heredity, chemicals, viruses and radiation. This research suggests a possible link between heredity and susceptibility to cancer-causing chemicals in the environment. Research is being focused on the development of more rapid and less costly testing methods and on the establishment of computer systems to help in determining the testing priority of chemicals. A total of 450 suspect chemicals are now being tested to determine the carcinogenic effects of chemicals. The isolation of a virus from cells of a human patient with acute myelocytic leukemia was recently reported. This may be the first successful isolation of human cancer virus. Current studies in the field of virology are exploring cancer-causing factors in DNA and RNA viruses and their possible relationship to genetic influences in the development of cancer.

The goal of detection and diagnosis research is to identify cancer in patients early enough and precisely enough so that application of the latest methods of treatment can have maximum effect on the control of the disease. Better diagnosis can be developed, applied and many lives saved through early diagnosis long before effective and practical methods are available to prevent cancer. There are three general aspects of cancer diagnosis where research has been emphasized: (1) Detection; (2) Diagnosis; (3) Prognosis. All three areas include laboratory research but are firmly based on patient studies, because clinical trials of new methods determine the effectiveness of these methods.

Usually the determination of the organ site and exact location of the cancer in a patient is provided by diagnostic x-ray. Two new methods are under investigation which show promise for helping to determine the organ site and location of the cancer: (a) computer-assisted tomography, which gives a cross-sectional x-ray of the body; and (b) a flexible fiberoptic endoscope which has greatly improved the capability to locate cancer in the lung, the stomach and the large bowel.

The goal of treatment research is to develop the means to cure as many patients as possible and to maintain maximum control of the cancerous process in patients not cured. This objective includes the following approaches: development and application of therapy; acquisition of antitumor drugs; reversion of the neoplastic process; beneficial enhancement of the immune mechanism; dissemination of research information related to advances in treatment; and development of the epidemiology of treatment, and identification of individuals likely to benefit from specific types of therapy.

Advances made in cancer treatment include the development of combination drug therapy for control of cancers of the breast, lung, ovaries and colon, and of Hodgkin's disease and non-Hodgkin's lymphomas. Other clinical studies have indicated that treatment by combinations of surgery and radiation and by drug combinations with radiation may be effective for some forms of cancer.

Major studies are being conducted in immunotherapy to develop a way to strengthen the immune system. Other clinical studies in the area of immunotherapy are focused on stimulating the body's natural immune system to destroy cancerous cells. A new system for screening large numbers of potential new

drugs has been initiated which requires significantly smaller quantities of materials and animals than conventional screening protocols and should simplify the identification of these new drugs.

Cancer biology has been defined as that research which cannot reasonably be identified specifically with a single research thrust, but which has potential application to all of the research thrusts. The need and importance of providing fundamental scientific information necessary for increasing existing knowledge of the cause and control of cancer in man has been emphasized. An impressive array of opportunities and leads in basic biological, chemical and related scientific fields has been provided through biomedical research. Two basic events are under study in Cancer Biology: (1) the transformation of a normal cell into a malignant one, involving alteration of nuclear DNA by viruses and other carcinogenic factors; and (2) tumor growth and spread from transformed malignant cells, which involves the mechanism of action of abnormal genes and the alterations in the structure and products of the malignant cell that allow it to avoid the body's normal, primarily immunological defenses.

Because of the importance of fundamental cell research, the NCI has established a Molecular Control Working Group. Achievements in this field such as the successful creation of an artifical gene, the transfer of genes from one animal species to another, studies in cell membrane and protease activity and findings made in the area of cell growth and composition and in the structure of white blood, all have significance for the eventual control of cancer.

The Cancer Centers Program began in 1962 with the initiation of the Cancer Clinical Research Centers. The program was based on the premise that the medical school, specialized cancer institutes and practicing physician must all participate in an integrated endeavor for the most effective cancer treatment and research effort. The National Cancer Act Amendments of 1974 provided impetus to the program when it amended the National Cancer Act of 1971 by deleting reference to the limit placed on the number of comprehensive cancer centers and strengthened the authority for construction and upgrading of cancer research facilities.

Continued emphasis will be placed on development of research manpower in 1976 in order to meet the broad objectives of the National Cancer Program. Training in eight major research areas will be emphasized; carcinogenesis, epidemiology, radiation, viral oncology, immunology, drug development, chemotherapy and tumor biology. The Clinical Education Program initiated in 1975, will be expanded to improve efforts in cancer education and teaching at both the undergraduate and graduate levels in schools of medicine, dentistry, public health, osteopathy and in specialized cancer institutions.

Cancer Control is among the highest priorities of the National Cancer Program and is organized into three major intervention areas: prevention; detection, diagnosis and pretreatment evaluation; and treatment, rehabilitation and continuing care. Prevention activities currently center around projects directed toward the reduction of lung cancer, the Nation's Number 1 cancer killer among men. Detection, diagnosis and pretreatment evaluation activities are directed toward projects for the early detection of breast cancer and lung cancer; cervical cytology screening; education programs in diagnostic radiology; and approaches to diagnosis for use by family physicians. The activities of the treatment, rehabilitation and continuing care intervention are directed toward programs in clinical chemotherapy; genital tract cancer; radiation physics centers; breast cancer, and head and neck cancer treatment and rehabilitation networks; integrated cancer rehabilitation services; training of physical and occupational therapists; and studies of patterns of care.

All Cancer Control activities are implemented through a variety of resources including cancer centers, medical schools and community cancer groups. More importantly, all activities are closely coordinated with the health care programs and activities of other federal agencies and state and local governments.

Recognizing the desirability of focusing all related efforts on a common goal, the National Cancer Act of 1971 assigned to the Director, NCI, the responsibility for coordinating the overall national effort against cancer. An Interagency Coordinating Committee has been organized to provide the necessary perspective for coordination of federal efforts in cancer research and the reduction of the cancer disease burden. At present, fourteen federal agencies are represented on the committee.

The NCI has established an Office of International Affairs and is expanding its cooperative efforts in the international sphere. Through the International Cancer Research Data Bank (ICRDB) progress has been made toward the exchange of cancer research information. The NCI also conducts a major communication program for the public and health professionals through the Office of Cancer Communications. The OCC program encompasses activities in the areas of public and professional information and education, and comprehensive collaboration with all communications media. This program ensures effective coordination of the dissemination of cancer knowledge to all participants in the National Cancer Program. Programs are being formulated to ensure that the latest advances in basic and applied research in the prevention, detection, diagnosis and treatment of cancer and the rehabilitation of cancer patients are available with a minimum of delay to the medical community and the public at large.

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DHEW - National Institutes of Health

CROSSWALK - 1975 ESTIMATE COLUMN 1976 PRESIDENT'S BUDGET

National Cancer Institute
(In thousands of dollars)

Program	Research Grants			Training Programs		Intramural[1/] Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Cancer Control	Construction	Total[2/]
	Regular Program	Specials Cancer Centers	Specials Other	Grants	Fellowships						
1975 Obligations											
A. Research Thrust											
1. Cause and prevention research	$21,230	$13,975	$5,062			$16,078	$94,870	$12,880			$164,095
2. Detection and diagnosis research	2,619	10,733	4,294			8,275	21,312	6,992			54,225
3. Treatment research	63,768	38,286	8,603			21,984	76,025	14,334			223,000
4. Cancer biology	47,523	25,932	666			11,379	7,967	12,533			106,000
Subtotal	135,140	88,926	18,625			57,716	200,174	46,739			547,320
B. Resource Development											
1. Cancer centers support		26,908						314			27,222
2. Research manpower development			5,000	$10,097	$12,066			439			27,602
3. Construction								542		$45,010	45,552
Subtotal		26,908	5,000	10,097	12,066			1,295		45,010	100,376
C. Cancer Control								1,002	$50,375		51,377
Total Obligations	$135,140	$115,834	$23,625	$10,097	$12,066	$57,716	$200,174	$49,036	$50,375	$45,010	$699,073

1/ Includes Collaborative Research and Support.
2/ Includes $7,712,000 carried forward from 1974 appropriation.

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1976 PRESIDENT'S BUDGET

National Cancer Institute
(In thousands of dollars)

Program	Research Grants			Training Programs		Intramural[1/] Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Cancer Control	Construction	Total
	Regular Program	Specials: Cancer Centers	Specials: Other	Grants	Fellowships						
1976 Estimate											
A. Research Thrust											
1. Cause and prevention research	$17,190	$11,465	$4,071			$17,647	$83,467	$13,360			$147,200
2. Detection and diagnosis research	2,475	8,598	3,193			9,369	15,156	8,199			46,990
3. Treatment research	49,498	35,508	5,645			24,502	63,360	16,887			195,400
4. Cancer biology	45,436	23,295	666			12,435	6,864	13,704			102,400
Subtotal	114,599	78,866	13,575			63,953	168,847	52,150			491,990
B. Resource Development											
1. Cancer centers support		21,833						408			22,241
2. Research manpower development			2,928	$5,168	$12,995			461			21,552
3. Construction								637		$22,000	22,637
Subtotal		21,833	2,928	5,168	12,995			1,506		22,000	66,430
C. Cancer Control								1,022	$45,558		46,580
Total Obligations	$114,599	$100,699	$16,503	$5,168	$12,995	$63,953	$168,847	$54,678	$45,558	$22,000	$605,000

1/ Includes Collaborative Research and Support.

National Cancer Institute

Budget Mechanism

	1975 Estimate			1976 Estimate		
	No.	FTE[1]	Amount	No.	FTE[1]	Amount
Grants						
Regular						
Non-competing	1,121		$75,555,000	1,090		$79,874,000
Competing	887		59,585,000	462		34,725,000
Renewal	(345)		(25,274,000)	(196)		(15,323,000)
New	(542)		(29,956,000)	(266)		(15,909,000)
Supplemental			(4,355,000)			(3,493,000)
Subtotal	2,008		135,140,000	1,552		114,599,000
Special						
Cancer research centers	182		115,834,000	141		100,699,000
Task forces	161		12,000,000	105		8,950,000
Research career program	84		2,000,000	85		2,000,000
Scientific evaluation	---		375,000	---		375,000
Clinical education program	84		5,000,000	49		2,928,000
Radiation development	3		4,250,000	2		2,250,000
Subtotal	514		139,459,000	382		117,202,000
Total Grants	2,522		274,599,000	1,934		231,801,000
Fellowships						
Non-competing	160	160	1,829,000	541	541	7,797,000
Competing	671	671	10,237,000	360	360	5,198,000
Renewal						
New	(671)	(671)	(9,325,000)	(360)	(360)	(5,198,000)
Supplemental			(912,000)			
Subtotal	831	831	12,066,000	901	901	12,995,000
Training Grants						
Non-competing	109	700	10,097,000	47	360	5,168,000
Competing						
Renewal						
New						
Supplemental						
Subtotal	109	700	10,097,000	47	360	5,168,000
Intramural Laboratory and Clinical Research			19,250,000			21,607,000
Research and Development Contracts			200,174,000			168,847,000
Collaborative Research and Support			38,466,000			42,346,000
Research Management and Program Services			49,036,000			54,678,000
Construction			45,010,000			22,000,000
Cancer Control			50,375,000			45,558,000
TOTAL			699,073,000			605,000,000

1/ Full-time equivalents

Research

Authorizing Legislation - Public Health Service Act, Title IV, Parts A and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	1,809	$40,378,000	1,755	$42,038,000	-54	+$1,660,000
Other expenses	---	506,942,000	---	449,952,000	---	-56,990,000
Total	1,809	547,320,000	1,755	491,990,000	-54	-55,330,000
Subactivities:						
Cause and Prevention Research	581	164,095,000	577	147,200,000	-4	-16,895,000
Detection and Diagnosis Research	272	54,225,000	264	46,990,000	-8	-7,235,000
Treatment Research	567	223,000,000	529	195,400,000	-38	-27,600,000
Cancer Biology	389	106,000,000	385	102,400,000	-4	-3,600,000
Total	1,809	547,320,000	1,755	491,990,000	-54	-55,330,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	---	75,555,000	---	79,874,000	---	+4,319,000
Competing	---	59,585,000	---	34,725,000	---	-24,860,000
Special	---	107,551,000	---	92,441,000	---	-15,110,000
Cancer Research Centers	---	(88,926,000)	---	(78,866,000)	---	(-10,060,000)
Task Forces	---	(12,000,000)	---	(8,950,000)	---	(-3,050,000)
Intramural Laboratory and Clinical Research	512	19,250,000	505	21,607,000	-7	+2,357,000
Research and Development Contracts	---	200,174,000	---	168,847,000	---	-31,327,000
Collaborative Research and Support	909	38,466,000	882	42,346,000	-27	+3,880,000
Research Management and Program Services	388	46,739,000	368	52,150,000	-20	+5,411,000
Total	1,809	547,320,000	1,755	491,990,000	-54	-55,330,000

The research pursued by the National Cancer Institute can be classified into the areas of cause and prevention research, detection and diagnosis research, treatment research and cancer biology. Research conducted within these areas is pursued in accordance with the objectives and approaches defined in the National Cancer Program Plan. This represents a balanced program covering the entire spectrum of research, from basic through applied and developmental. These activities are performed through grants, contracts and in-house research.

Cause and Prevention Research

Cause and prevention research is primarily concerned with finding and eliminating those elements that cause cancer, as well as identifying the factors that determine the susceptibility of certain individuals to these elements. An extension of this primary concern is to develop preventive measures to control human cancers as these causative agents are discovered. Within the scope of the National Cancer Program Plan, cause and prevention research has four major objectives. These objectives are to develop the means: (1) to reduce the effectiveness of external agents for producing cancer; (2) to modify body mechanisms so as to minimize the hazards of cancer-inducing agents; (3) to prevent transformation of normal cells to cells capable of forming cancers; and (4) to prevent progression of precancerous cells to cancers, the development of cancers from precancerous conditions, and the spread of cancers from primary sites. Research is conducted on an intramural basis at the NIH, at the Government-owned/contractor-operated Frederick Cancer Research Center, and in collaboration with educational institutions, government agencies, non-profit organizations, and industrial concerns. This research is performed throughout the United States and in several foreign countries.

A major portion of the resources committed to cause and prevention research is utilized on projects designed for reducing the effectiveness of external agents for producing cancer (Objective 1 of the National Cancer Program Plan). Principal areas of activity are: (1) bioassay studies by in vivo, in vitro, and host-mediated methods for environmental screening; (2) the establishment of a number of information systems, including the implementation of a coherent methodology for the selection of chemicals for bioassay and a computerized data system for records maintenance and data evaluation of the testing programs; (3) the investigation of smoking habits and modified tobacco products in order to identify susceptible individuals and develop a less hazardous cigarette; (4) epidemiologic studies on the frequency and distribution of cancer in man (an interesting example is a case-control study in the Hawaiian-Japanese, a population undergoing displacement from low to high colon cancer risk because of Western-type diet, which has uncovered important correlations between food items and bowel cancer); (5) the search for viruses or virus genetic information which may be causally related to the initiation of human cancer; (6) the role of various agents in co-carcinogenesis and basic studies contributing to a better understanding of the mechanisms of action of these agents; (7) characterization of newly isolated candidate human tumor viruses; (8) nutritional studies including determinants of susceptibility or resistance, the role in treatment, long-term management, and rehabilitation of the cancer patient; and (9) identification of factors involved in the phenomena of resistance and susceptibility of cells and of hosts to tumor viruses.

Additional cause and prevention research which is directed toward Objectives 2, 3, and 4 of the National Cancer Program Plan includes: (1) epidemiologic studies of various cancers in large populations to identify high-risk groups. In breast cancer, for example, studies are in progress for the possible usefulness of various markers together with their relation to the type of breast cancer, in the identification of high-rick groups; (2) studies marking the progression of a normal cell to the cancerous state, with emphasis on changes in the cell membrane associated with malignancy. Such research might lead to therapeutic means of interrupting the cancerous process or serve as the basis for improved means for the early detection of cancer; (3) in vitro model systems developed for the study of tissue response to carcinogen exposure and the

application of these systems to human tissues. The identification of host factors which affect the carcinogenic response is being pursued in these systems, and factors capable of inhibiting the carcinogenic process are being identified and studied: (4) an expanded program in the area of pancreatic cancer, now under way, for which models have been developed. These models, previously lacking, provide a much needed base for studies on the pathogenesis and prevention of this tumor type; (5) development of additional programs in endocrine and childhood cancer; (6) new emphasis on the study of carcinogen metabolism and toxicology, with efforts now under way to investigate the formation, environmental distribution, metabolic activation, and mechanism of action of N-nitroso compounds; and (7) the field of environmental carcinogenesis where extensive consultation and documentation have been provided on the problems of evaluation of risk in environmental carcinogenesis.

The 1976 level, a decrease of $16,895,000 from 1975 will allow continued activities, however, at reduced levels to include research in the following areas: production of viruses necessary to conduct studies, including characterization of two candidate human cancer viruses (possible breast cancer virus and leukemia virus), as well as efforts to search for other human cancer viruses; assessment of carcinogenic potential of environmental and industrial chemicals; development of in vitro and host-mediated studies required for short-term bioassays of chemical carcinogens; field testing of a hypothesis about environmental and industrial causes of cancer, such as asbestos in the Duluth, Minnesota water supply; development of cancer epidemiology study centers as area resources, in addition to serving in the evaluation of cancer control programs; development of drugs that may be useful in reducing the smoking habit, and smoke cessation techniques; study of the role of nutrition in causation of cancer, such as caloric intake, diet composition, diet deficiencies, alcoholism, food preservation, and food preparation; study of the problem of competition for available nutrients between the host and the tumor; and study of the mechanisms of action of cancer-causing agents and the alteration of host response to cancer-causing agents.

The following are highlights of Cause and Prevention Research accomplishments during the past year:

Virus Cancer Research. The isolation of a virus from cells of a human patient with acute myelocytic leukemia was reported recently. The virus appears to be of human origin and is immunologically and biochemically similar to other viruses which cause myelocytic leukemia and other cancers in primates. This may be the first successful isolation of a human cancer virus. Using tumor viruses as probes, viral genes have been shown to be present in normal cells of many vertebrate species, including higher primates and man. This demonstrates that information which may code for malignant transformation is present in cells in the form of viral genetic material. Breakthroughs in the techniques of growing large-scale quantities of two cancer viruses (mouse mammary tumor virus and Epstein-Barr virus) will for the first time provide enough of these viruses for extensive studies. The provirus theory of RNA viral oncogenesis has been strengthened by the demonstration that purified DNA from transformed cells, even those which produce no virus, can transmit the infection to normal cells.

Carcinogenesis Research. The number of potentially carcinogenic chemicals under test in animals is about 450 and includes many of industrial and environ-

mental significance. Standard protocols and data collection and analysis systems for large-scale bioassays have become operative; a major effort was made in providing pathology reference standards for the evaluation of carcinogenic effects. A new coordinated program has been implemented for the further development and validation of in vitro short-term testing methodologies. Validation of a battery of such assays will greatly increase the rate at which substances suspected to cause cancer can be evaluated. Development of this area will have great impact on the ability of industry to pretest new products, of regulatory agencies to monitor environmental hazards, and of science to understand basic mechanisms of cancer causation and their inhibition. Experimental animal models have been developed for the induction of cancer of the pancreas, for which no model previously existed. This accomplishment opens the way to the study of a type of cancer which current knowledge affords little hope of survival. A number of studies are focused on the relationship of nutritional factors and carcinogenic effects. Tobacco research has defined cigarette characteristics that can be modified to produce less hazardous smoke such as type of tobacco, quality of paper, contribution of nicotine to toxicity, etc. The tobacco program has developed specific bioassays capable of assessing the toxic capacity of smoke, thereby defining the criteria for less hazardous cigarettes that may be recommended for human consumption. A nutrition program was initiated by assembling an advisory group of experts, collecting state-of-the-art information, and sponsoring conferences and workshops to define areas of needed research and action.

Field Studies & Statistics. For the first time, U.S. cancer mortality by county (1950-1969) has been published as well as an atlas showing each county's risk of cancer of various sites. Clusters of excessive mortality were identified for certain cancers providing leads to occupational and other environmental hazards. The risk of various cancers among recipients of kidney transplants was clarified, and this is providing insights into the role of immunity in cancer etiology. Various families in which cancer aggregated excessively were studied to define syndromes and subclinical precancerous states. Deficiencies were described in various claims that Hodgkin's disease is infectious among family members and the drinking water from the Mississippi River is causing an increase in cancer in the New Orleans area. The epidemiologic component of the U.S.-Japan Cooperative Cancer Research Program was developed, and a tumor surveillance program was established in Nagasaki to parallel one previously initiated in Hiroshima for studies of cancer after atomic bomb exposure. The results of the Third National Cancer Survey has been published. An overview of available information from the Survey has been published including data on duration and initial cost of hospitalization. The SEER (Cancer Surveillance Epidemiology and End Results Reporting) Program, a program which provides information on the magnitude of the cancer problem in the United States, on the variation in the rate of incidence over time and among sub-groups of the population, and on factors associated with variation in patient survival, continues to provide data for planning and evaluating cancer control programs and for assessing the impact of cancer center activities designed to improve the quality of diagnostic and treatment services.

Frederick Cancer Research Center. A group working on endocrine carcinogenesis and one on procedures for safe handling of carcinogens, has been established. Hundreds of thousands of animals have been produced and supplied for experiments at the Center and throughout the National Cancer Program. The basic cancer research program has been initiated and will direct research toward: (a) cellular as well as systemic aspects of carcinogenesis; (b) host defense mechanisms against the establishment of neoplastic clones; (c) immunobiology of viral and chemical carcinogenesis with respect to the etiologic agents, prevention of establishment of neoplastic clones, and the regulation of tumors; and (d) a project emphasizing the biology of tumor metastatsis.

Detection and Diagnosis Research

The goal of detection and diagnosis research, described in Objective 5 of the National Cancer Program Plan, is to develop the means for accurate assessments of (a) the risk of developing cancer and (b) the presence, extent and probable course of existing cancers. Seven general approaches to this goal are identified in the National Cancer Program Plan, and these can be grouped into three areas: detection, diagnosis and prognosis. Detection includes the identification of population groups with high-risk of cancer (approach 5.1); the identification of conditions associated with cancer (approach 5.2); the development of procedures for screening population groups of cancer (approach 5.3); and the prediction of individuals who will get cancer (approach 5.5). Diagnosis research is the improvement of procedures to determine the presence and location of cancer in individuals (approach 5.4). Prognosis is the determination of cancer characteristics that cause different growth rate and probability of spread; it is an attempt to predict the course of cancer in individuals (approach 5.6). The public acceptance of prevention, screening and detection methods (approach 5.7) is part of the Cancer Control Program.

Detection. The problem of detection is to find, among vast numbers of apparently healthy people, the small number who have cancer. We cannot hope to do this for everyone through regular medical practice; annual check-ups even to the older half of the population in whom most cancers occur would overload existing medical facilities. There are two research approaches to solve this problem. The first, based on epidemiological studies of cancer incidence, aims to identify high-risk groups in whom detection procedures should be applied preferentially. Age, sex and environmental factors, such as cigarette smoking or exposure to some chemicals, can be used to select such groups, but better criteria are needed.

The second research approach to facilitate cancer detection is the development of new cancer tests and in the improvement of existing ones. The goal is a very simple test that can be applied to very large numbers of people. Such a test should be very specific and accurate, so that it will not miss some cancers or give many false positive reactions. The development of such tests involves three areas, immunology, biochemistry and cytology. Immune reactions are so sensitive that minute amounts of antigen broken off the surfaces of small cancers (or the antibody produced to neutralize that antigen) may be identifiable in blood specimens. Because these reactions are highly specific, they can also be used in diagnosis. The basic problem is the isolation and purification of tumor specific antigens from human cancers as a starting point for test development. This is a very difficult area since the antigens seem to be an integral part of the cell surface membrane, but encouraging progress has been made. There also seem to be other products of the cancer cells circulating in the blood which may possibly be used for cancer detection and diagnosis, such as abnormal hormones, proteins, peptides or enzymes. These belong to the field of cancer biochemistry. Analytical techniques are now available to distinguish such substances from closely related normal products, but correlations with clinical cancer are just beginning. Cytology has already proven itself in the detection of cancer of the uterine cervix. Clinical trials are in progress for its value in cancer of the lung and bladder, and it may be applicable in bowel cancer. This method is highly specific for cancer, but is more difficult to apply to large populations than a blood test, because cytologic smears must be obtained from a specific accessible part of the body. The present short supply of trained technicians to read the cytologic smears, will receive help through a major effort, now in progress, to develop machines to assist in reading

these smears. Prototype equipment is being tested to sort out cancer cells from normal cells, and progress is being made in the development of machines to read smears by computer-assisted pattern recognition techniques.

A most important aspect of research on new methods of cancer detection is exact proof of their clinical effectiveness. Many new tests can identify patients with advanced cancer, but they break down in marginal cases or in screening of apparently normal people. Beyond the problems of specificity and sensitivity, there is another question which must be considered before justifying the great expense of nationwide screening programs, namely, will such early detection actually improve the survival from cancer? This has been proven in cytologic screening for cancer of the uterine cervix and in x-ray mammography for cancer of the breast, but in some kinds of cancer the disease may begin in several places at once or spread very early to distant sites so that early detection would not affect survival. Therefore, a long-term clinical trial is a necessary test of all promising new detection methods.

Diagnosis. This program seeks ways to tell if cancer is present or not in a single patient, and if present, to attempt to locate exactly where it is. Immunologic and cytologic tests, diagnostic x-ray technique (i.e. computer-assisted tomography), ultrasonic scanning, nuclear magnetic resonance, and endoscopy provide valuable tools for the early diagnosis of potential cancer patients.

Prognosis. The prediction of the probable growth of cancer, its spread and response to treatment in an individual patient is an integral part of the clinical management of the disease. Research in this area requires detailed analysis of the clinical and laboratory findings at the time of operation correlated with the response to surgery, the effects of radiation and chemotherapy, and survival.

The 1976 level, a decrease of $7,235,000 from 1975 will allow continued activities, however, at reduced levels to include those described below:

Detection. In immunology, effort will continue in the identification and purification of new tumor-associated antigens; antibodies produced by the body; detection of circulating antigen-antibody complexes in cancer patients; and the detection and characterization of virus-related antigens, antibodies and other potential cancer markers.

Diagnosis. The efforts in immunology and virology described under Detection are expected to have application to cancer diagnosis as well. There will be projects involved with the diagnostic radiology of cancer, largely to capitalize on the recent development of computer-assisted transaxial tomography (CTT) for the diagnostic localization of brain tumors.

Prognosis. Research in this area will be involved in the standardization of reporting procedures so that correlations of diagnostic information, treatment procedures, clinical course and survival of patients involved in the clinical research aspects of the Cancer Centers Program around the nation could be made.

The following are highlights of Detection & Diagnosis Research accomplishments during the past year:

Research has been conducted into the use of the flexible fiberoptic endoscope in localizing lung tumors resulting in precise localization of otherwise non-visualized tumors. Evaluation of breast fluid obtained by a special pump has been initiated which may lead to a useful detection technique for breast cancer. Two instruments are being developed for breast cancer detection without exposure to x-ray.

It is now possible to predict which patients with advanced breast cancer will respond favorably to surgical removal of the sources of estrogen (ovaries, adrenals and pituitary gland) by testing for estrogen-binding protein in the tumor itself. Predicted responders can thus be treated without delay, and those with no estrogen-binding protein can be spared these operations and assigned to some other treatment.

In a large clinical trial on the detection of lung cancer in heavy smokers prior to development of symptoms, using sputum cytology and chest x-ray, the early results show much smaller cancers than in patients with symptoms.

Over 25 potential immunodiagnostic tests for cancer were evaluated last year with the aid of a bank of stored serum specimens. In one evaluation, a test for a new purified fraction of carcinoembryonic antigen (CEA), was positive in some 50 percent of patients with gastrointestinal cancer with very few false positives. This high level of discrimination is a major advance in improving the CEA test and in cancer immunodiagnosis.

Treatment Research

Cancer is most often a systemic disease; even patients curable by local forms of treatment, such as by surgery or radiation have been shown to shed cancer cells into the blood stream. These cells fail to establish themselves and grow in long surviving patients either due to some inherent defect in the cell itself or the host's ability to prevent cancer-cell growth through its own defense mechanisms. On the other hand, over half of all patients who develop one of the many types of cancers die of it each year, even though in many cases it appeared to be localized. In these patients their own defenses are unable to control the circulating malignant cells and systemic treatment is required to control the wide-spread growth.

It was this realization (that cancer is most often a systemic disease) that led to the research thrust for the development of systemic treatment (drugs for cancer) 20 years ago. Ten years ago the realization that cancer cells were often considered foreign by the host's immune system and the host's defenses could be modulated and used to alter or control cancer growth led to the additional interest in immune therapy. These therapies have been tested in patients with far advanced cancer. Their success in some such patients has led to the current interest of researchers in applying them to patients with apparently localized disease with a high-risk of recurrence of cancer. Thus the treatment thrust has reached a turning point. With each report of individual successes in advanced cancer it becomes more and more possible to mobilize the private medical community and the patient resources necessary to apply 20 years of investment in therapeutic research where it will do the most good.

The National Cancer Program formalizes these concepts under Objective 6 of the National Cancer Program Plan. The goal of Objective 6 is "to develop the means to cure as many patients as possible and to maintain maximum control of the cancerous process in patients not cured". This objective includes the following approaches: development and application of therapy; acquisition of antitumor drugs; reversion of the neoplastic process; beneficial enhancement of the immune mechanism; dissemination of research information related to advances in treatment; and development of epidemiology of treatment; and identification of individuals likely to benefit from specific types of therapy.

The 1976 level, a decrease of $27,600,000 from 1975 will allow continued activities, however, at reduced levels to include: research in the development and utilization of methodologies of immunotherapy, chemotherapy, surgery and radiation (alone and in combinations) for the cure and palliation of cancer because it is felt that systemic and local therapies have reached the point where wide-spread application is possible in the majority of patients who develop cancer in the United States. In part these studies of combined modalities have been successfully initiated and carried out in some cancers (breast cancer, lymphocytic and histiocytic lymphomas, Hodgkin's disease, leukemias, osteogenic sarcoma).

The specific projects under Objective 6 which will receive priority for funding in 1976 are as follows:

In breast cancer funds will be provided to continue the current trials of post operative therapy with L-PAM, CMF (a drug combination), and immunotherapy

in patients with positive lymph nodes. The surgical study to define the optimal surgical treatment will continue.

In colon cancer clinical trials of adjuvant chemotherapy with drugs and immunotherapy with MER-BCG will be initiated at a modest level.

In ovarian cancer comparative trials of surgery followed by chemotherapy or radioisotope treatment in patients with Stage I disease will be initiated. Following surgery in patients with Stage II disease, radiation therapy with chemotherapy will compare to radiation therapy alone.

Phase II and III trials of drugs and new types of immunotherapy in various common cancers will be continued at various cancer centers throughout the country.

Support will be provided to continue the intramural research effort in Ewing's sarcoma.

Collaborative arrangements for clinical trials of new drugs, immunotherapy, combined modalities, high LET radiation and new schemes of radiation time-dose-volume fractionation will be continued.

The following are highlights of Treatment Research accomplishments during the past year:

A test of the relative merits of radical versus less radical surgical procedures in breast cancer, with or without the addition of post-operative radiation therapy, has given preliminary indications of the possible equal effectiveness of the less mutilating procedure. If the current trend persists, these results should lead to significantly less morbidity associated with the surgical treatment of breast cancer.

Most patients with breast cancer present to their doctors what appears to be localized disease. Eighty percent of those patients with tumor in the lymph glands at surgery have recurrence. A study utilizing post-operative treatment with phenylalanine mustard (L-PAM) in such patients has shown a significant decrease in recurrences up to two years after surgical removal of the tumor.

Since there are many drugs with some effect in advanced breast cancer, various combinations have been tested to develop a safe and effective one which might be expected to be even more effective than L-PAM when used post-operatively. Such a combination (cytoxan, methotrexate, 5-Fluorouracil, (CMF)) has been tested in patients with advanced cancer of the breast, compared to L-PAM in such patients, and shown to be more effective. This combination has been under test as an adjuvant in patients who have tumor positive lymph glands after surgical treatment. Preliminary evidence suggests it will prove even more effective than L-PAM as adjuvant treatment.

The first effective drug combination in the treatment of advanced colon cancer has emerged which should be applied as adjuvant post-operative treatment. The combination consists of two drugs (Vincristine and 5-Fluorouracil) and a recent drug developed by the Drug Development Program of NCI--methyl CCNU. If this therapy is successfully applied, it could make a significant impact on the 70,000 patients who die of colon cancer each year.

Progress was reported in the treatment of advanced malignant melanoma (a relatively rare form of skin cancer) by chemoimmunotherapy -- a combination of an anticancer drug and a killed bacterial vaccine, which stimulates the immune defense system of the patient.

New leads have emerged in ovarian cancer, the fifth most common cancer killer of women. A drug (hexamethylmelamine) developed by NCI has shown to be effective and when compared to the standard treatment, perhaps the most effective single agent in patients with advanced ovarian cancer. Identification of the success of L-PAM (the standard treatment) in patients with advanced ovarian cancer (10 percent long-term survivors) opens the way to adjuvant treatment of early disease, as in breast cancer.

The new drug, Adriamycin, became commercially available. It has wide-spread usefulness in cancer treatment and has been incorporated in treatment plans for breast cancer, bone cancer, other sarcomas, and lymphomas. Adriamycin has shown to be effective in the hertofore drug resistant tumor, bladder cancer.

Osteogenic sarcoma, a tumor of bone of young people, has until this time been fatal in 80 percent of patients within two years after apparently successful removal of the cancer. With the use of post-operative drug treatment with either high dose methotrexate followed by an antidote (citro-vorum factor), or Adriamycin, the drug mentioned above, the two year survival has been increased from 20 to 80 percent.

Patients with the virulent tumor, reticulum cell sarcoma (diffuse histiocytic lymphoma), have been shown to be curable (up to 9 years disease-free survival) with drug combinations. The application of these combinations to patients with early disease in conjunction with radiotherapy is now being tested.

An RNA virus has been identified in patients with acute myelocytic leukemia which closely resembles a tumor virus of apes and monkeys. The ability to grow this virus in quantity and generate antibodies and vaccines from it, and the identification of group specific proteins on the surface of cells infected with the virus open up new and exciting areas of epidemiologic research and treatment of this disease.

Advances were made in the use of biological markers -- substances found in the blood or urine correlating with the presence of a tumor -- to determine the extent of breast cancer.

The use of drugs and x-ray therapy together in Ewing's sarcoma has led to markedly improved survival of patients afflicted with this disease.

A multidisciplinary approach using surgery, radiation and two drugs has greatly improved the outlook for long-term survival of patients with Wilms' tumor, a cancer of the kidney.

The addition of immunotherapy to chemotherapy in patients with acute myelocytic leukemia has led to an increase in the number of persons remaining alive and free of leukemia when compared to the use of drugs alone.

Heat appears to affect cancer cells more severely than normal cells. The inability to safely control the temperature of patients with cancer has led to the failure of the application of heat as a therapeutic modality. New work suggests that cancer cells may be selectively heated using microwave technology.

Cancer Biology

The overall goal of Cancer Biology is to provide for a better understanding of the fundamental, molecular and cellular processes with the expectation that better methods will result for the prevention, detection, diagnosis and treatment of cancer.

There are two basic events under study in Cancer Biology. First, is the transformation of a normal cell into a malignant one, involving the alteration of nuclear deoxyribonucleic acid (DNA) by viruses and other carcinogenic factors. The second event is tumor growth and spread from transformed malignant cells. This involves the mechanism of action of abnormal genes, and the alterations in the structure and products of the malignant cell that allow it to avoid the body's normal, primarily immunological defenses.

Studies are conducted in most of the basic biological fields and represent particular aspects of pathology, cell biology, molecular biology, genetics embryology, ultrastructural analysis, kinetics, morphogenesis, developmental biology, immunology and other disciplines which may be of primary concern to the Cancer Biology Program. Cancer Biology is basic to each of the other cancer program thrusts and constitutes the basic research nucleus which is essential for the implementation of the National Cancer Program.

The 1976 level, a decrease of $3,600,000, will allow continued activities, however, at reduced levels to include: (1) understanding of the fundamental mechanism of metastasis from cancerous cells which could lead to improved methods of control; (2) acquiring knowledge of biological, physical and chemical properties of cell surfaces and membranes through multidisciplinary approaches; (3) developing a clearer understanding of the role of viruses in the etiology of human cancer; (4) exploring the mechanisms by which tumors avoid destruction by the immune system and ways of rendering antigens more antigenic by treating cells with biologically active compounds. Also, there is need for further development of better animal model systems for immunological studies. Sound information in these areas is essential for the application of recently developed immunological techniques for diagnosis, treatment and prevention of cancer.

Effort is needed to define the chemical, enzymatic and ultrastructural differences between metastatic tumors of varying potential to form secondary growth *in vitro*. A popular theory is that metastatic potential of tumor cells is determined by their cell surface properties. The problems of membrane biology are complex and must be attacked by the use of a combination of approaches from various disciplines.

The following are highlights of Cancer Biology accomplishments during the past year:

Significant contributions have been made in the investigation of multiple aspects of genetics and biochemistry in areas of spontaneous and induced mutation in cell cultures. Optimal conditions are provided for growth of particular cell species and refined techniques for establishing cell cultures from a single cell and for the quantitative investigation of immunoglobulin synthesis.

Recently devised lipid vesicles which can be placed into cells now can be used for incorporating pharmacologically active substances at specific cell surfaces or other regions of the cell for possible modification of cellular behavior. The usefulness of such innovative techniques is potentially of high significance in controlling or reversing certain cancer processes.

The Molecular Control Working Group has been established to explore the knowledge of fundamental molecular mechanisms for control of cellular transformation. This group is composed of eminent biological and molecular scientists whose objective is to keep close surveillance of the area to insure that promising research leads in molecular control are converted into practical application as quickly as possible.

Continued progress has been made in the past year in (1) understanding the mechanism and refining techniques for the experimental use of non-specific adjuvants such as BCG for possibly increasing immune responses and (2) using mediators such as immune RNA and transfer factors in producing specific immunity to tumors. These areas of investigation are providing considerable insight in understanding immunological systems and processes.

The Frederick Cancer Research Center is now serving a vital role in producing a variety of resources (such as cell lines, serum, viruses, laboratory animals, etc.) which are distributed to many participants of the cancer program.

In a recent finding, a neutral factor isolated from contact-inhibited melanocytes restored normal growth to malignant melanocytes in vitro. This finding may represent a fundamental mechanism for regulation of normal cell and possible applications to control of tumor growth.

One of the major problems in mammary cancer research has been the difficulty involved in culturing human breast cells. A routine system for cultivation of these cells is now available and should contribute immensely to human breast cancer investigations.

Resource Development

Authorizing Legislation - Public Health Service Act, Title IV, Parts A and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	38	$770,000	32	$830,000	-6	+$60,000
Other expenses		99,606,000		65,600,000		-34,006,000
Total	38	100,376,000	32	66,430,000	-6	-33,946,000
Subactivities:						
Cancer Centers Support	16	27,222,000	14	22,241,000	-2	-4,981,000
Research Manpower Development	10	27,602,000	8	21,552,000	-2	-6,050,000
Construction	12	45,552,000	10	22,637,000	-2	-22,915,000
Total	38	100,376,000	32	66,430,000	-6	-33,946,000
Budget Mechanism:						
Research Grants						
Special	---	31,908,000	---	24,761,000	---	-7,147,000
Fellowships	---	12,066,000	---	12,995,000	---	+929,000
Training Grants	---	10,097,000	---	5,168,000	---	-4,929,000
Research Management and Program Services	38	1,295,000	32	1,506,000	-6	+211,000
Construction	---	45,010,000	---	22,000,000	---	-23,010,000
Grants	(---)	(30,000,000)	(---)	(17,000,000)	(---)	(-13,000,000)
Contracts	(---)	(15,010,000)	(---)	(5,000,000)	(---)	(-10,010,000)
Total	38	100,376,000	32	66,430,000	-6	-33,946,000

In augmenting the research conducted by the Institute, this area contains Cancer Centers Support, Research Manpower Development and Construction. The Cancer Centers Support Program is designed to: determine the feasibility of establishing new centers; generate planning efforts to ensure maximum participation of the medical community served by the centers; help support administrative activities of the center; and provide funds for developing new programs within the center. The Research Manpower Development area supports research training and education in scientific fields related to cancer research. Construction monies provide the resources required for the modernization and renovation of existing space for cancer laboratory and clinical research purposes, as well as new construction for biohazard facilities.

Cancer Centers Support

The Cancer Centers Support Activity of the National Cancer Institute's Centers Program refers to Core Grants and Exploratory Grants. Together, these grants fund the central integrative and structural resources of centers, both human and physical, and their essential developmental functions. Grant dollars in support of research performed at cancer centers are reflected under the appropriate research areas of Cause and Prevention Research, Detection and Diagnosis Research, Treatment Research and Cancer Biology.

Core Grants are awarded in support of the costs of key senior personnel, administration, central services and facilities, and to provide seed money for the developmental phases of new cancer programs within the centers. Only a small part of the operational costs of a center is actually furnished by these Core Grants; the major portion is supplied by combinations of individual research grants, clinical and basic center program grants, cancer control grants, clinical education and training grants, fellowships, contracts and various funds generated by the centers themselves from local and other federal and non-federal sources.

Exploratory Grants are designed to determine the feasibility and optimal methods of establishing, expanding or integrating cancer center activities. They support the planning efforts essential to ensure maximum participation of local scientists and practicing physicians, and provide plans to develop needed community involvement and outreach programs.

In summary, the Cancer Centers Support Activity is designed to promote multidisciplinary research and to serve as a resource for the implementation of improved knowledge about cancer prevention, early detection, multidisciplinary diagnosis, multimodal treatment and rehabilitation. Its goal is a fully developed, geographically balanced network of Cancer Centers which can interact with each other and with other institutions in their local areas to accelerate the nationwide attack upon cancer.

As a result of the continued growth and improvement in Cancer Centers during the past year, over half of the country's population now has access by means of one day or less in surface transportation time to and from a major multidisciplinary center for purposes of consultation or for an outpatient visit for those patients referred to a center for special treatment. Physicians located in community hospitals in these areas can easily consult with the center investigators who are in their own specialty fields. Projects are under way in many of these centers and in the planning phase in others to increase cancer training, professional and lay education, and public information services in their surrounding areas. Programs of data gathering and exchange are also under development to benefit the entire network of centers and provide improved data on a national scale. In several regions where there are many cancer investigators and facilities, the Centers Program has encouraged the formation of inter-institutional affiliations or area cancer councils representing various combinations of medical schools, hospitals, civic leaders, and health associations.

Research Manpower Development

Research Manpower Development consists of several training programs. These programs include Clinical Training, Graduate Research Training, Fellowships, the Clinical Education Program and the National Research Service Award Program.

The Clinical Training Program includes grants awarded to medical, dental and osteopathic schools in order to advance the caliber of education in cancer-related subjects. The Graduate Research Training Program consists of predoctoral and postdoctoral training awards to institutions in various scientific disciplines to provide a source of competent research manpower. The Fellowship Program presents awards to qualified American citizens for postdoctoral research training in the basic or clinical sciences. These fellowships may be obtained in this country or while the scientist is abroad. The Clinical Education Program awards to educational institutions grants which help facilitate more innovative teaching programs related to cancer. The National Research Service Award Program awards individual postdoctoral fellowships and institutional grants in eight major research areas of importance to the National Cancer Institute. All but the Clinical Education Program and the National Research Service Awards Program are in a phase-out state.

Whereas $12,066,000 supported he training of 831 scientists in 1975 by means of the various research fellowships programs, $12,995,000 will be required in 1976 to meet the continuing commitments of these activities and to award fellowships authorized under the National Research Service Awards Program. Through these mechanisms, the National Cancer Institute anticipates modestly increasing the research trainee pool to 901 in 1976 in eight major research areas: carcinogenesis, epidemiology, radiation, viral oncology, immunology, drug development, chemotherapy and tumor biology.

Carcinogenesis, the first area, concerns the mechanisms whereby certain environmental chemicals cause cancer. New methods must be developed to test the potential carcinogenicity of the ever-increasing number of chemicals to which people are exposed. Moreover, innovative techniques are needed to detect cancer in people and animals in its earliest stages and to protect them against cancer induced by chemical carcinogens. To provide support for research scientists in this area, $2,099,000 will be required to train 162 trainees in 1976. This compares to 150 trainees at a cost of $1,952,000 in 1975.

As cancer control programs expand, the critical shortage of essential manpower in epidemiology becomes more acute. Trainees must have access to clinical records, laboratory facilities, computer capability and biometric and epidemiologic expertise relating to cancer. These resources are scattered among university departments so that individual students find it extremely difficult to negotiate well-balanced training of high quality. In 1975, seventeen trainees will be supported at $362,000, while in 1976, $397,000 will be required to train 20 epidemiologists and biometicians.

The Radiation Program develops new radiotherapeutic approaches, techniques and equipment. The program studies underlying biologic mechanisms and tissue tolerance. It carries out clinical trials with radiation alone

and with other modalities. Recent accomplishments in x-ray scanning, sub-atomic therapy, thermoradiotherapy, computer-optimized radionuclide ultrasonic scanning and treatment have generated an urgent requirement for additional research manpower. In 1975, 41 scientists in radiologic oncology disciplines will be supported at a cost of $645,000. Emphasis in this area will be increased in 1976 with 44 scientists trained at a cost of $700,000.

Viral oncology deals with the implicated role of viruses in the etiology of cancer. Studies are conducted at the cellular and molecular levels. These studies include investigations of gene expression and cell regulatory functions. There is a pressing need for scientists well-trained in biochemical and biological virology, so that the question of viral causation of human cancer can be further explored. In addition, new techniques must be devised for the diagnosis, prevention and treatment of viral-induced cancer. In 1975, $3,016,000 will train 207 scientists. In 1976, $3,238,000 will support the training of 223 viral oncologists.

Immunology is the newest discipline contributing to cancer treatment. Immunological knowledge is also necessary to the diagnosis and prevention of cancer. In 1975, 141 scientists will be trained at a cost of $1,931,000. For 1976, $2,076,000 will train 153 scientists in immunologic and immunotherapeutic techniques. It is expected that this area will be emphasized heavily in the future.

Drug development involves the synthesis and evaluation of chemicals which are maximally effective against cancer and minimally toxic to the patient. With increasing emphasis upon drug development, the continuing shortage of molecular pharmacologists is a deterent to the successful continuation of the program. To meet this need for trained pharmacologists, $1,363,000 will be spent in 1975 to train 99 scientists. In 1976, 108 scientists will receive training at an estimated cost of $1,468,000.

Chemotherapy encompasses the use of drugs in treating cancer. In 1976, the establishment of safe, effective dosages of drugs for use in extended clinical trials will be emphasized. It is estimated that 38 scientists will be trained at a cost of $655,000 in 1976, while in 1975, 34 scientists will be supported at a cost of $603,000.

The eighth research area, tumor biology, provides the fundamental knowledge of precancerous and cancerous lesions. This area of cancer research is essential to the future development of better diagnostic, preventive and therapeutic methods. 142 scientists will be trained in the basic biology of the cancer cell in 1975 at a cost of $2,194,000. In 1976, 153 scientists will be trained at a cost of $2,362,000.

In 1975, NCI expanded its efforts in the area of manpower by initiating the Clinical Education Program at a cost of $2,515,000. The $2,515,000 will support 42 grants in 1975, and in 1976, $2,928,000 will support 49 grants.

Finally, $5,168,000 will be required in 1976 (a reduction of $929,000 below the 1975 level) to continue the phase-out of Cancer Clinical and Graduate Training Programs.

Construction

Within the provisions of the National Cancer Act of 1971, as revised in 1974, the National Cancer Institute is authorized construction authority to provide new and expanded cancer research facilities including basic and clinical research and support facilities and biohazard control and containment laboratories. The National Cancer Institute pays up to 75% of the cost of construction in connection with cancer research centers. The construction funds are essential to the strengthening of research and demonstration programs by aiding in the development and dissemination of new, high quality multidisciplinary cancer research efforts.

In 1975, funds totalling $45,552,000 relate to construction projects, including awards at comprehensive and specialized cancer centers. The total funds represent $38,542,000 in current year funds and $7,010,000 carried over from 1974. The carryover includes $4,275,000 for the Norris Cotton Cancer Center.

In 1976, construction funds totalling $22,637,000 will be used for modernization and renovation of existing space for cancer laboratory and clinical research purposes, as well as new construction in connection with biohazard facilities. The Department of Labor, Occupational Health and Safety Standards, has established biohazard standards for facilities which support programs involving oncogenic viruses and chemical carcinogens. These containment facilities will minimize cross-contamination and prevent release of any potentially hazardous agents into the laboratory environment or to the surrounding community. With the 1976 funds, additional renovation and modernization projects will also be accomplished on the NIH campus and at the Frederick Cancer Research Center. The 1976 funds will improve clinical research space and laboratories relating to virology, carcinogenesis, immunology, chemotherapy and radiation therapy.

Cancer Control

Authorizing Legislation - Public Health Service Act, Title IV, Parts A and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	59	$950,000	49	$1,030,000	-10	+$80,000
Other expenses	---	50,427,000	---	45,550,000	---	-4,877,000
Total	59	51,377,000	49	46,580,000	-10	-4,797,000
Budget Mechanism:						
Research Management and Program Services	9	1,002,000	8	1,022,000	-1	+20,000
Cancer Control	50	50,375,000	41	45,558,000	-9	-4,817,000
In-House	(50)	(1,700,000)	(41)	(1,900,000)	(-9)	(+200,000)
Contracts	(---)	(44,275,000)	(---)	(39,150,000)	(---)	(-5,117,000)
Grants	(---)	(4,400,000)	(---)	(4,500,000)	(---)	(+100,000)
Total	59	51,377,000	49	46,580,000	-10	-4,797,000

The National Cancer Institute's Cancer Control Program is responsible for the development, implementation, and evaluation of all cancer control activities as established under the National Cancer Act of 1971. This Program also serves as the focal point for all NCI activity in rehabilitation, both research, and control. The goal of Cancer Control is to effect the rapid and effective application of present and new knowledge from research to both the public and health professionals in the community setting in order to prevent the occurrence of cancer, minimize its impact, and reduce the number of cancer deaths. The Cancer Control Program, a "people" oriented program, is attempting to get the newest and the best information to the widest audience possible through several specific operations. These operations include field testing, demonstrating, promoting and evaluating new and existing methods and techniques. Cancer Control carries out its activities with a wide variety of audiences including the public, the community physicians and community health professionals in their environments of community hospitals and health organizations, medical societies, medical schools, cancer centers, voluntary organizations and state and local governmental agencies. The Program's activities are carefully coordinated to avoid duplication of existing activities in the community setting.

In concert with the other segments of the National Cancer Program, Cancer Control concentrates its efforts on three major intervention areas: (1) Prevention; (2) Detection, Diagnosis, and Pretreatment Evaluation; and (3) Treatment, Rehabilitation, and Continuing Care. Though Cancer Control is not involved in wide-spread health care delivery for all cancer patients, its activities are related to those segments of the private health community and the Federal government involved in total health care delivery.

The specific objectives of the intervention areas are:

Prevention. To assure that practical and effective methods and techniques

of cancer prevention are available to and utilized by health professionals. It is generally recognized that prevention, when possible, is the most effective and efficient means of controlling cancer.

Detection, Diagnosis, and Pretreatment Evaluation. To assure: (1) that with the aid of health professsionals and other groups there will be continuous assessment of current practices and development of principles for the detection, diagnosis and pretreatment evaluation of cancer patients; (2) that practical and effective cancer screening/detection methods and techniques are available to and utilized by populations at risk; (3) that optimal methods for the diagnosis and pretreatment evaluation of cancer are available and utilized by persons with precancerous and cancerous lesions.

Treatment, Rehabilitation, and Continuing Care. To assure: (1) with the aid of health professionals and other groups, the continuous assessment of current practices and the development of principles for the treatment of cancer patients; (2) optimal treatment and follow-up care methods and techniques are available to and utilized by cancer patients; (3) optimal rehabilitation methods and techniques are available to and utilized by cancer patients; and (4) optimal palliative and supportive care methods and techniques are available to and utilized by patients with recurrent and/or disseminated cancer.

The 1976 level, a decrease of $4,797,000 will allow continued activities, however, at reduced levels. Programs will continue in breast cancer detection demonstrations, cervical cancer screening demonstrations, community outreach projects and other areas presently being studied.

The following are highlights of Cancer Control accomplishments and initiatives during the past year:

In the area of breast cancer, Cancer Control has developed 27 demonstration projects co-funded with the American Cancer Society for the early detection of breast cancer. These projects will screen a total of 270,000 asymptomatic women during the first two years of the project. The modalities used for detection include: physical examination, mammography (xeroradiography), and thermography. Preliminary results have shown that 77 percent of women proven to have cancer are free of cancer in the axillary nodes. Under routine detection methods, in previous projects, 49 percent of the women proven to have cancer were shown to be free of cancer in the axillary lymph nodes. This, therefore indicates a potential improvement of 28 percent utilizing these new methods for the early detection of breast cancer.

Another major effort of Cancer Control in the area of breast cancer includes the development of community hospital networks for the diagnosis, treatment, rehabilitation, and continuing care of women with proven breast cancer. Twelve such networks have been organized to develop optimal control demonstration activities and each network is to manage at least 175 new cases of breast cancer per year for a total requirement of 2100 cases of breast cancer.

Programs in Pap screening for the early detection of cervical cancer have been initiated through State and Territorial Health Departments. By the end of Fiscal Year 1975, over half of the State and Territorial Health Departments in the United States will be involved in the cervical screening program and it is expected that 500,000 women will be screened for cervical cancer, using NCI supported funds. The objectives of this program are to foster the development of trials in the areas of greatest need to include populations at the highest risk of the disease whose participation in the past programs has been negligible or absent. Another purpose of these programs will be to accomplish rigorous evalua-

tions to permit the definition of the efficacy of cervical cancer screening programs on populations at highest risk and to determine those means of recruiting such difficult-to-reach populations in the most practical, effective and acceptable manner. The ultimate goal is to define, demonstrate, and promote the means and methods whereby these effective detection programs can be implemented on a continuing basis by local health care providers.

An important new initiative in Fiscal Year 1975 was the development of Community-Based Cancer Control Programs. These projects are characterized by three major ingredients: (1) a cooperative community arrangement of all important components related to cancer including cancer centers, medical schools, practicing physicians, and voluntary groups; (2) population based data systems; and (3) the ability to take on modern cancer control activities. These programs require each to serve a population from one and one half to three million people. The program is divided into two phases, planning and implementation. This year, 33 communities have submitted planning proposals and 5 have submitted implementation plans which are currently under review. It is estimated that 40 to 60 million people could be affected by this program which is designed to demonstrate and promote the use of all the latest tested intervention techniques and procedures for the control of cancer in a concerted and unified manner combining community resources, i.e., manpower, money, and facilities with those of the National Cancer Institute in a manner beneficial to the community and the Institute.

Important to the goals of Cancer Control, especially at the community level, is information related to resources necessary to carry out cancer control. Determinations of total monetary costs related to cancer and needed manpower resources to carry out cancer control activities have been initiated and are to be completed within 18 to 24 months. Additional sources of funding, other than NCI, which could be used to support community programs are presently under review. The implementation phase requires a 50 percent matching of funds from the community being supported by Cancer Control.

Certain populations are at highest risk to cancer. In addition to indigenous factors related to cancer, certain individuals are at higher risk to the development of cancer due to exposure to potentially carcinogenic substances. Exposure may occur through industrial/environmental sources or inadvertently through exposure to some substance or drug used in therapy. A number of projects related to high-risk populations have been initiated. One is related to the follow-up and detection of 850 asbestos workers for the development of early lung cancer. Another involves the regular examination of from 4000 to 5000 girls who were exposed in utero during their mother's pregnancy to diethylstilbestrol. Both projects involve secondary prevention with health education being an important activity.

Diagnostic and therapeutic radiology represent important intervention modalities in cancer. In order to effect the highest grade of radiology, Cancer Control has initiated six radiologic physics centers, to be coordinated through the American Association of Physicists in Medicine, to carefully monitor all field test and demonstration projects of Cancer Control in the community setting for both diagnostic and therapeutic radiology.

In order to effect the participation of community hospitals, projects have been directed specifically to them and involve the community oncologist, family practitioners and other community health professionals. Community hospital networks for certain disease specific cancer sites are under way including activities for acute childhood leukemia and lymphoma, and both Hodgkin's and non-Hodgkin's lymphoma. Each network will develop diagnosis, treatment and rehabilitation for 350 to 500 new patients per year. In the area

of head and neck cancer, additional networks have been developed and each of these networks will analyze approximately 200 new cases of head and neck cancer per year.

One of the major objectives of cancer control is the continuous assessment of current practices in diagnosis, treatment, and rehabilitation. To assess therapy practices and develop optimal approaches, a grant has been awarded to the American College of Radiology for a national evaluation of their membership of radiation oncologists. From this study information will be collected to determine the current methods of treatment by radiation. Criteria for optimal radiation therapy at the community level are being developed.

A Cancer Control Communication Network has been established through each designated Comprehensive Cancer Center. To fully implement the goals of this Communication Network, i.e., to provide the public with access to a resource center where they can obtain appropriate information and education on cancer, a wide area telecommunication system (WATS) will be implemented through American Telephone and Telegraph System. Every state in the United States and Puerto Rico will have access to this system. Each person in the United States can benefit from this system through increased awareness leading to appropriate action.

Rehabilitation is an important concept in the current Cancer Control activity. Rehabilitation will ensure the cured and controlled cancer patient return to as normal a life as possible. Projects are under way for the demonstration of integrated rehabilitation in a number of hospital settings -- both cancer center, medical center, and community hospital settings, as well as at home. Projects have been initiated to educate special health professionals for oncology rehabilitation and include occupational and physical therapists and maxillofacial prosthodontists.

Rehabilitation not only includes physical restoration but also involves psychosocial and vocational considerations. Five demonstration projects to effectively deal with the psychological problems of the cancer patient and his family have been initiated. Behavioral studies to determine motivational factors which inhibit patients from utilization of proper detection or prevention methods or promote delays in seeking appropriate diagnosis or inability to carry out prescribed treatment programs have been initiated. Behavioral considerations form an important matrix to all Cancer Control activities.

As progress is made in cancer, more cancer patients will require gainful employment after recuperation. Employment practices are being studied in order to determine the extent of the problem, the best means of overcoming employer biases, and to demonstrate in a concerted fashion in a number of industries the proper employment practices related to cancer patients.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Cause and prevention research (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
581	$164,095,000	$898,500,000[1/]	577	$147,200,000

Purpose: Included within this activity is the national program for research contained in the first four objectives of the National Cancer Program Plan. These objectives are: (1) to reduce the effectiveness of cancer producing agents; (2) to modify body mechanisms so as to minimize the hazards of cancer inducing agents; (3) to prevent transformation of normal cells to cells capable of forming cancers; and (4) to prevent progression of precancerous cells to cancers, the development of cancers from precancerous conditions, and spread of cancers from primary sites.

Explanation: Research in this area is conducted in government laboratories and in academic and private institutions. Research in the academic and private sector is accomplished through the funding of both research grants and research and support contracts. Cause and prevention research includes viral, carcinogenic, and demographic research. Those selected activities that are performed within the breast, lung, large bowel, bladder and prostate task forces are also identified within this research area.

Accomplishments in 1975: 1) The isolation of a virus from cells of a human patient with acute myelocytic leukemia was reported recently. This may be the first successful isolation of a human cancer virus. 2) Tobacco research has defined cigarette characteristics that can be modified to produce less hazardous smoke. 3) Certain herpesviruses have been found to cause cancer in primates. 4) A new coordinated program has been implemented for short-term testing methodologies for environmental carcinogens. 5) The large-scale production of oncogenic viruses for use by researchers throughout the country has been established at the Frederick Cancer Research Center.

Objectives for 1976: Research will be continued, however, at reduced levels to include: research in the search for other cancer viruses; field testing for environmental and industrial causes of cancer; development of drugs that may be useful in reducing the smoking habit and smoke cessation techniques; and studies of the role of nutrition in the causation of cancer, such as caloric intake, diet deficiencies, alcoholism, food preparation and food preservation.

1/ For all programs of NCI including $68,500,000 for Cancer Control.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Detection and diagnosis research (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
272	$54,225,000	$898,500,000[1/]	264	$46,990,000

Purpose: As described in Objective 5 of the National Cancer Program Plan, the goal of detection and diagnosis research is to develop the means for accurate assessments of (a) the risk of developing cancer in individuals and in population groups and (b) the presence, extent and probable course of existing cancers.

Explanation: Identified with the goals of this research are three general areas of investigation; detection, diagnosis and prognosis. In the area of detection the goal is to find, among vast numbers of apparently healthy people, the small number who have hidden cancer. In the area of diagnosis, research is centered on the improvement of methods for determining the presence and location of cancer in individuals. In the prognosis area, research is concerned with the prediction, in an individual patient, of the growth, spread and response to treatment of his cancer. Research in detection and diagnosis is carried out in government laboratories and in academic and private institutions through the funding of research grants and research and support contracts.

Accomplishments in 1975: 1) Research results now show that by testing for estrogen-binding protein in patients with advanced breast cancer, the decision to surgically remove the sources of estrogen (ovaries, adrenals and pituitary gland) or to assign the patient to some other treatment can be done without delay. 2) Evaluation into the use of independently developed machines for the automated analysis of cancer cytology specimens has been conducted. 3) Research has continued on the development of an ultrasonic scanner for use in detecting breast cancer. 4) Over 25 potential immuno-diagnostic tests for cancer have been evaluated with the aid of a bank of stored serum specimens. 5) Work has continued on a technique for diagnosis of brain tumors by use of computer-assisted tomography. 6) Research has been started, investigating the preparation of cervical smear specimens more suited to analysis by instruments than are present Pap smears. 7) In a large clinical trial, using sputum cytology and chest x-ray, the early results in detecting lung cancer in heavy smokers prior to the development of symptoms show much smaller cancers than in patients with symptoms.

Objectives for 1976: Research will be continued, however, at reduced levels. Evaluation will continue of machines developed for reading cancer cytology specimens. The use of the self-obtained vaginal smear as a valuable screening technique will be investigated.

1/ For all programs of NCI including $68,500,000 for Cancer Control.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Treatment research (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
567	$223,000,000	$898,500,000[1/]	529	$195,400,000

Purpose: Included within this activity is the national program for research in treatment of patients with cancer. The primary goal of Objective 6 of the National Cancer Program Plan is to "develop the means to cure as many patients as possible and to maintain control of the cancerous process in patients not cured". The National Cancer Institute serves as the focal point for research in cancer treatment in this country and probably the world.

Explanation: Research in this area is conducted in government laboratories and in academic and private institutions. Research in the academic and private sector is accomplished through the funding of both research grants and research and support contracts. Efforts are under way to expand existing and initiate additional clinical cooperative groups to investigate anti-cancer therapies. Research treatment by the use of surgery, radiation, immunotherapy and chemotherapy either used singly or in combination is a major segment of present research efforts.

Accomplishments in 1975: 1) The relative merits of less radical surgical procedures in breast cancer, with or without post-operative radiation therapy, have been tested and preliminary results indicate the possible equal effectiveness of the less mutilative procedure. 2) The first effective drug combinaton in the treatment of advanced colon cancer has emerged as adjuvant post-operative therapy. 3) The two year survival rate of patients with osteogenic sarcoma has been increased from 20 to 80 percent with the use of combined modality treatment. 4) An RNA virus has been identified in patients with acute myelocytic leukemia. The ability to grow this virus in quantity and generate antibodies and vaccines from it opens up new areas of epidemiologic research and treatment of this disease. 5) The addition of immunotherapy to chemotherapy in patients with acute myelocytic leukemia has led to an increase in the number of persons remaining alive and free of leukemia when compared to the use of drugs alone.

Objectives for 1976: Research will be continued, however, at reduced levels. Current trials of drug combinations following breast cancer surgery will be continued. Phase II and III trials of drugs and new types of immunotherapy will be continued at various cancer centers throughout the United States.

1/ For all programs of NCI including $68,500,000 for Cancer Control.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Cancer biology (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
389	$106,000,000	$898,500,000[1/]	385	$102,400,000

Purpose: The overall goal of Cancer Biology is to provide for a better understanding of the fundamental, molecular and cellular processes with the expectation that better methods will result for the prevention, detection, diagnosis and treatment of cancer.

Explanation: The focus of Cancer Biology encompasses essentially two broad areas of concern. The first is the transformation of a healthy cell into one that is malignant, and involves the alteration of nuclear deoxyribonucleic acid (DNA) by such entities as viruses and other carcinogenic agents. The second major area of concern is that of tumor growth and spread from transformed malignant cells.

Accomplishments in 1975: Significant contributions have been made in the investigation of the multiple aspects of genetics and biochemistry in areas of spontaneous and induced mutation in cell cultures. A routine system for cultivation of human breast cells is now available and should contribute immensely to human breast cancer investigations. Continued progress has been made in the past year in understanding the mechanisms and refining techniques for the experimental use of non-specific adjuvant treatment such as BCG for possibly increasing immune responses and using mediators such as immune RNA and transfer factors in providing specific immunity to tumors.

Objectives for 1976: Research will be continued, however, at reduced levels. Continuation of the overall goals of Cancer Biology through specific objectives will continue including: (1) providing for an increased understanding of the fundamental mechanisms of metastatsis from cancerous cells which could lead to improved methods of control; (2) acquiring more detailed knowledge of biological, physical and chemical properties of cell surfaces and membranes through multidisciplinary approaches; and (3) developing a clearer understanding of the role of viruses in the etiology of human cancer.

1/ For all programs of NCI including $68,500,000 for Cancer Control.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Cancer centers support (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
16	$27,222,000	$898,500,000[1/]	14	$22,241,000

Purpose: The cancer centers support activity includes exploratory projects and core grants. Exploratory projects are designed to determine the feasibility of establishing specialized and comprehensive cancer centers. Core grants are used to assist in the support of the administration, common services and collaborative activities of cancer centers.

Explanation: Comprehensive Cancer Centers are established to conduct long-term multidisciplinary programs related to cancer. The dollars for research performed at cancer centers are reflected under the appropriate research areas of Cause and Prevention Research, Detection and Diagnosis Research, Treatment Research and Cancer Biology. The core grant assists in the operating and administrative expenses of these centers. Exploratory projects, awarded through the grant mechanism, also assist in the planning and development aspects prior to the establishment of a cancer center.

Accomplishments in 1975: Currently, the NCI has recognized 17 Comprehensive Cancer Centers. This includes three Comprehensive Centers that were identified before the National Cancer Act of 1971 was passed. Planning is now under way in many areas throughout the country to determine the feasibility of the establishment of cancer centers. In 1975, 25 core grants will assist in the support of the operating and administrative expenses of the comprehensive and specialized centers.

Objectives for 1976: Research will be continued, however, at reduced levels. Feasibility studies for cancer centers will continue. Continued emphasis will be placed on cor- support for cancer centers commensurate with the expansion and development of the cancer centers program.

1/ For all programs of NCI including $68,500,000 for Cancer Control.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Research manpower development (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
10	$27,602,000	$898,500,000[1/]	8	$21,552,000

Purpose: The Research Manpower Development Program provides for fellowships and training grants in various scientific fields related to cancer research, as well as the Clinical Education Program which is designed to create more innovative education programs in medical schools.

Explanation: Through the use of the grant mechanism, awards are made to individuals (in the form of fellowships) and to institutions in support of training and education programs in the sciences related to cancer research.

Accomplishments in 1975: During 1975, the Institute awarded 831 fellowships and 109 graduate and clinical training grants. These awards included such disciplines as carcinogenesis, epidemiology, radiation, viral oncology, immunology, drug development, chemotherapy and tumor biology.

Objectives for 1976: It is estimated that approximately 901 individuals will be supported through fellowship awards. In addition, the Clinical Education Program will provide resources for the award of 49 grants including awards to schools of medicine, dentistry, and osteopathy.

1/ For all programs of NCI including $68,500,000 for Cancer Control.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Construction (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
12	$45,552,000	$898,500,000 1/	10	$22,637,000

Purpose: Within the provisions of the National Cancer Act of 1971, as revised in 1974, construction authority was provided to the National Cancer Institute. This authority is to provide new and expanded cancer research facilities including basic and clinical research and support facilities and biohazard control and containment laboratories.

Explanation: Grant construction support is provided on a matching-fund basis for the construction of basic research laboratories, clinical research facilities, animal facilities and special biohazard containment facilities. The rate of Federal grant participation is up to 75 percent of the eligible construction costs with the remaining 25 percent being provided by the grantee from non-Federal sources. Contract construction support is included in the budget for improving facilities on the NIH campus and at the Frederick Cancer Research Center.

Accomplishments in 1975: In 1975, $45,552,000 supported the upgrading and construction of cancer research facilities at various comprehensive and specialized centers. This includes $7,010,000 in carryover funds from 1974 including one project involving earmarked funds for the Norris Cotton Cancer Center of $4,275,000. Additional renovation and modernization projects are being accomplished on the NIH campus and the Frederick Cancer Research Center.

Objectives for 1976: Funds totalling $22,637,000 are requested for new construction, alteration and renovation of existing facilities and the completion of shell space to expand the national cancer research effort. Construction funds will include support to existing and potential comprehensive centers at various geographical locations, as well as new construction relative to biohazard containment facilities.

1/ For all programs of NCI including $68,500,000 for Cancer Control.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Program Purpose and Accomplishments

Activity: Cancer control (Public Health Service Act, Title IV, Parts A and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
59	$51,377,000	$68,500,000[1/]	49	$46,580,000

Purpose: Within the provisions of the National Cancer Act of 1971, was the establishment of the Cancer Control Program with the general purpose of bridging the gap between research and application in the practice of medicine and public health so as to minimize illness and death from cancer.

Explanation: The major objectives of the program are to take cancer research outputs in prevention, detection, diagnosis, treatment and rehabilitation and demonstrate their effectiveness in controlled community groups; communicate the successful R&D and demonstration findings to the practitioners of medicine and public health; educate practitioners and laymen about the latest cancer research findings; and stimulate the general application of effective control measures.

Accomplishments in 1975: In order to coordinate the Cancer Control Program with related activities at all government levels, a project is in process to review all legislation by Federal, State and local governments that may affect cancer control activities. Two projects involving exposure of special population groups to carcinogens are under way; one involves the study of asbestos workers for detection of precancerous lesions or early carcinoma of the lungs, the second involves regular examination of girls whose mothers received diethylstilbestrol (DES) during pregnancy. In an effort to reach high-risk medically indigent women, the Cancer Control Program expanded the cervical cancer screening projects.

Results from the nationwide breast cancer detection demonstration program indicates that the screening program is detecting earlier stages of breast cancer which leads to higher 5-year and 10-year survival rates for these patients. In cooperation with the Comprehensive Cancer Centers, nine projects were funded for the planning of community outreach programs. Projects are under way for the demonstration of integrated rehabilitation both in hospitals and at home.

Objectives for 1976: The Cancer Control Program will be maintained, however, at a reduced level. Programs will continue in breast cancer detection demonstrations, cervical cancer screening demonstrations, community outreach projects and other areas presently being studied.

1/ This is included in total authorization of $898,500,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation[1/]

	1976 Estimate	Interim Period
Appropriation	$605,000,000	$151,250,000
Total, Obligations	605,000,000	151,250,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $100,000; Interim period - $25,000.

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Research				
(a) Cause and prevention research	577	$147,200,000	577	$38,123,000
(b) Detection and diagnosis research	264	46,990,000	264	12,168,000
(c) Treatment research	529	195,400,000	529	50,610,000
(d) Cancer biology	385	102,400,000	385	26,517,000
Resource development				
(a) Cancer centers support	14	22,241,000	14	5,791,000
(b) Research manpower development	8	21,552,000	8	2,266,000
(c) Construction	10	22,637,000	10	4,120,000
Cancer control				
(a) Cancer control	49	46,580,000	49	11,655,000
Total obligations	',836	605,000,000	1,836	151,250,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	1,836	1,836
Full-time equivalent of all other positions	263	263
Average number of all employees	2,081	2,081
Personnel compensation:		
Permanent positions	$34,884,000	$8,721,000
Positions other than permanent	2,786,000	696,500
Other personnel compensation	1,020,000	255,000
Subtotal, personnel compensation	38,690,000	9,672,500
Personnel benefits	5,208,000	1,302,000
Travel and transportation of persons	3,419,000	779,750
Transportation of things	250,000	62,500
Rent, communications and utilities	1,700,000	425,000
Printing and reproduction	1,210,000	302,500
Other services:		
Project contracts	213,005,000	52,055,500
Payment to NIH Management Fund	20,757,000	5,189,250
Other	30,497,000	8,132,500
Supplies and materials	14,900,000	3,725,000
Equipment	3,900,000	975,000
Grants, subsidies and contributions	271,464,000	68,628,500
Total, obligations by object	605,000,000	151,250,000

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the National Cancer Institute consistent with the 1976 Estimate. No new program initiatives will commence during this period. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate. A summary of program efforts during the three-month interim period is as follows:

1. Research

A. Cause and Prevention Research efforts will continue to involve studies in the areas of carcinogenesis, viral oncology and epidemiology. Research is conducted on ways to reduce external agents; minimize the risk of cancer development in individuals; prevent the transformation of normal cells to cancer cells; and prevent the spread of the disease from primary sites.

B. Detection and Diagnosis Research will continue to involve the development of procedures for detecting population groups for cancer; improvement of methods to determine, in individual patients, the presence and exact location of cancer; and improved methods to predict, in an individual patient, the probable growth, spread, and response to treatment of cancer.

C. Treatment Research efforts will continue to develop the means to cure cancer patients and to control the progress of cancers utilizing surgery, radiation, chemotherapy, immunotherapy, and combination therapies. Also, research on new sources of chemical agents for use in treating cancer will continue.

D. Cancer Biology efforts will be directed to further investigations into the process of gene expression which may lead to better methods of characterizing the mechanisms by which genetic information is obtained; continued efforts to ensure that promising research leads in molecular control are converted into practical application rapidly; and further efforts on the fundamental mechanisms of invasiveness or metastasis in tumor cells.

2. Resource Development

A. The Cancer Centers Support program consists of two types of grants: exploratory grants, which are used to determine the feasibility of establishing cancer centers and to support planning efforts; and core grants which support the administration, common services and collaborative activities of cancer centers. Research conducted at centers is supported from the applicable research efforts in cause and prevention, detection and diagnosis, treatment and cancer biology.

B. The Research Manpower Development activity supports research training and education in scientific fields related to cancer research.

C. Construction funds will be used for modernization and renovation of existing space for cancer laboratory and clinical research purposes, as well as new construction in connection with biohazard facilities.

3. Cancer Control

This activity will continue to bridge the gap between the discovery of effective research findings and their application in the practice of medicine and public health by supporting specialized demonstration activities, including education and training programs.

THURSDAY, APRIL 10, 1975.

NATIONAL HEART AND LUNG INSTITUTE

WITNESSES

DR. ROBERT L. RINGLER, ACTING DIRECTOR
DR. RONALD LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
RAYMOND M. KUEHNE, ACTING EXECUTIVE OFFICER, NATIONAL HEART AND LUNG INSTITUTE
JOHN H. REEDER, FINANCIAL MANAGEMENT OFFICER, NATIONAL HEART AND LUNG INSTITUTE
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. The committee will be in order.

We will continue with the National Institutes of Health, and we have today the National Heart and Lung Institute. The presentation will be made by Dr. Robert L. Ringler, the Acting Director.

We have a biographical sketch of you, Doctor, which we will place in the record at this point.

[The biographical sketch follows:]

Name: Robert L. Ringler, Ph. D.

Position: Acting Director, National Heart and Lung Institute.

Birthplace and date: Chase, Mich., March 27, 1922.

Education: A.B.—Central Michigan College—February 1951, Ph. D.—(biochemistry) Michigan State University—August 1955.

Experience: 1961–present, National Heart and Lung Institute, NIH, Bethesda, Md.; April 1974–present, Acting Director; 1972–1973, Acting Director, Division of Blood Diseases and Resources; 1969–present, Deputy Director; 1969–1790, Acting Associate Director for Collaborative Research and Development; 1968–1969, Special Assistant to the Director; 1967–1968, Chief, Institutional Research Programs; 1967–1968, Acting Chief, Program Projects Branch; 1966–1967, Head, Task Force on Cardiovascular Research Centers; 1962–1966, Chief, Program Projects Branch; 1961–1962, Scientist Administrator; 1957–1961, Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit, Mich., senior associate, enzyme division; 1955–1957, North Carolina State College, Raleigh, N.C., assistant professor, department of biochemistry; and 1951–1955, Michigan State University, East Lansing, Mich., graduate assistant.

Association memberships: American Society of Biological Chemists; American Heart Association; Fellow, American College of Cardiology; and Sigma Xi.

Special awards, citations, or publications: 75th Anniversary Award, Central Michigan University, 1967; DHEW Superior Service Honor Award, June 1970; and author or coauthor of approximately 25 scientific publications.

Mr. FLOOD. Do you have some people with you that you want us to know?

Dr. RINGLER. Yes.

I have Mr. John Reeder, who is the Institute's Financial Management Officer, and on his left Mr. Raymond Kuehne, who is the Acting Executive Officer of the Institute.

Mr. FLOOD. I see you have a prepared statement, Doctor. How do you want to handle it?

Dr. RINGLER. If you will, I will read it at this time.

Mr. FLOOD. All right.

Dr. RINGLER. Mr. Chairman and members of the committee, I am pleased to have this opportunity to present my statement in support of programs in heart, blood vessel, lung, and blood diseases and blood resources. The Institute will be submitting a detailed report on its activities and accomplishments as required by Public Law 92-423 and the National Heart and Lung Advisory Council has also submitted its report as required by the same act. In my comments here I would like to summarize a few highlights from these reports.

NATIONAL HEALTH PROBLEM

The importance of the Institute's research programs relates directly, of course, to the fact that in terms of incidence and mortality, the diseases to which they relate continue to be the primary health problem in the United States. Some 28 million Americans are afflicted with some form of heart or blood vessel disease. In 1972, over 1 million Americans died from heart and blood vessel diseases. This represented more than 54 percent of deaths from all causes. Moreover, they cost the economy more than $30 billion per year in lost productivity and expenses for medical care.

Diseases of the lung constitute a major national health problem of increasing dimensions. They account for an estimated 150,000 deaths each year, cause 60 million days lost from work, 40 million days of bed-restricted activity, and cost the economy some $12 billion a year.

Despite these figures, I appear before you with a high order of optimism. For the first time since the begining of this century we are seeing a decline in the mortality rate from heart attacks in the United States. This was reported to you last year based on 1972 data. Provisional data for 1973 support this trend. This I believe is a tribute to the research that has been done on understanding disease mechanisms, new diagnostic and treatment methods including surgical treatment, introduction of coronary care units, better understanding of heart disease risk factors, and so on.

EMPHYSEMA

In the area of lung disease—emphysema during the 1950's and early 1960's was the single fastest rising cause of death in the United States.

Mr. FLOOD. What is emphysema?

Dr. RINGLER. It is a chronic disease of the lung which in effect makes the lung unable to do its work in terms of being able to exchange oxygen to supply the body.

Mr. FLOOD. Is it a virus? Is it organic? What is it?

Dr. RINGLER. No. The etiology, the cause, in other words, of the disease is really not known, to be truthful with you. It is thought to be associated with a number of factors, one of which may be a hereditary tendency to be more susceptible to it.

Other causative factors are associated with it.

Mr. FLOOD. Could it possibly be hereditary?

Dr. RINGLER. To a degree, I believe, it is hereditary and by that I mean an increased susceptibility to the disease.

Mr. FLOOD. Is this a cancer of any kind?

Dr. RINGLER. The answer is "No."

This increase in mortality began to level off during the mid-1960's and there has been no further increase in mortality from emphysema since 1969 although we have not experienced an actual decline in deaths from the disease.

I am also pleased to report that significant research progress and achievements have been made since passage of the National Heart, Blood Vessel, Lung, and Blood Act of 1972. These offer new opportunities which will ultimately improve the outlook for those millions of Americans, whom I have enumerated, who suffer from these diseases, or who are at risk of developing them. I would like to briefly outline a few of these programs.

DISSEMINATION OF KNOWLEDGE—HIGH BLOOD PRESSURE

Many studies indicate that more aggressive application of existing knowledge will materially reduce disability and death from the complications of heart, blood vessel, lung, and blood diseases. In response to this the Institute has initiated a prevention, control, and education program in each of these diseases. The aim is to develop better mechanisms, using all media of communication, to disseminate knowledge about these diseases to the general public and to the medical profession.

Perhaps the best example of progress in this area is within the area of high blood pressure. The national high blood pressure education program, which NHLI coordinates, involves about 100 national, State, and local organizations.

Mr. FLOOD. What is hypertension?

Dr. RINGLER. High blood pressure.

Mr. FLOOD. That is a good answer. I thought it was, you know. That is why I asked you. Somebody has to ask it.

Dr. RINGLER. High blood pressure is something we think affects about 23 million Americans. It is a major risk factor for other forms of heart and vascular disease.

Mr. FLOOD. You use the term high blood pressure and hypertension interchangeably.

Dr. RINGLER. Yes, sir. I guess I tend to use the word "hypertension."

Mr. FLOOD. That is all right.

Dr. RINGLER. Public awareness is increasing about the importance of regular blood pressure checks and of regular taking of medication for those found to be hypertensive. Many communities have launched high blood pressure detection and followup programs. To assist communities, the Institute offers a "community consultation service" to provide general guidelines, advice on pitfalls to be avoided, and suggestions about other resource groups to aid in total community efforts. Educational materials are available to such groups from the Institute's High Blood Pressure Information Center. To date, over 300 communities have taken advantage of this service.

NATIONAL RESEARCH AND DEMONSTRATION CENTERS

The Institute awarded its first three National Research and Demonstration Centers during the past year—one in heart and vascular diseases, one in lung diseases, and one in blood resources.

Mr. FLOOD. What are the vascular diseases as distinguished from a heart disease and/or lung disease?

Dr. RINGLER. Vascular disease would be a disease that affects the arteries or veins of the body as opposed to disease that affects the heart or the lungs.

Each center includes programs in fundamental research, clinical research and clinical application, and provides an environment conducive to the training of young scientists. In addition, their purpose is to facilitate and expedite the application of research findings to practical patient care. Each of the centers has an active program of public and professional education.

Other specific education approaches are being newly supported. In the Division of Lung Diseases, for example, a contract program is developing an educational program for professional and paraprofessional personnel who are likely to be the first contact with patients suffering from acute respiratory insufficiency. The Division of Blood Diseases and Blood Resources is pursuing a similar effort in devising an educational approach to assist physicians in the most efficient use of blood products for blood component therapy.

ASPIRIN-MYOCARDIAL INFARCTION STUDY

Just getting underway is a large-scale clinical study to determine if the regular ingestion of aspirin reduces the incidence of recurrent heart attacks in men and women who have already had a heart attack. This is called the aspirin-myocardial infarction study. Pilot studies have been successfully undertaken and some 4,000 patients will be enrolled during the next year in 30 clinical centers. These patients will be observed for 3 years while on study medication.

CORONARY ARTERY STUDY

Aortic-coronary artery bypass is a surgical means of treating severe coronary heart disease by routing blood around the obstructions in diseased coronary arteries. This technique, placement of a bypass graft around a narrowed or occluded coronary artery, brings increased blood supply to endangered heart muscle. It has been extensively developed and widely practiced with over 25,000 operations in the past year alone. In a substantial majority of patients with severe angina pectoris (chest pain from heart disease), the procedure results in relief of symptoms. Whether symptomatic relief persists over the years and whether the procedure reduces the risk of future heart attacks and improves long-term survival remain to be determined. A collaborative trial to assess these factors is going through the pilot phase preparatory to a full-scale trial.

ISCHEMIC HEART DISEASE

For a number of years the Institute has supported an extramural research program directed specifically at improved understanding, prevention, and treatment of heart attack or myocardial infarction. The single largest part of this program has been the myocardial infarction research units which combine broad programs of clinical research with fundamental laboratory studies and developments in relevant technology and investigative methods. Much of the improvement in the understanding and treatment of heart attack over the past several years has come from these units. As an outgrowth of that program, to build upon it, and broaden the scope of research, the Institute has implemented a program of Specialized Centers of Research on Ischemic Heart Disease. The objective of this program is multidisciplinary clinical and fundamental research directed at the reduction of death and disabiilty from all forms of ischemic heart disease, including not only heart attacks, but also chronic forms of the disease including angina pectoris, rhythm disturbances, and heart failures. The new and expanded effort is also directed to techniques of rehabilitation following heart attack and problems of sudden cardiac death, since each year about 400,000 deaths from coronary heart disease occur before the patient reaches the hospital. About half of these occur almost instantaneously or unwitnessed.

LIPID RESEARCH CLINICS

As we have reported earlier, the Institute has underway a number of clinical trials concerning arteriosclerosis and high blood pressure. One of these, the Lipid Research Clinics program, was established to determine what proportion of the population has an abnormality of their blood fats, known as type II hyperlipoproteinemia, and who are, thereby, at a markedly increased risk of a heart attack during the early adult years. Over the last 2 years the Lipid Research Clinics Program has evaluated available technology and developed with industry rapid, inexpensive, accurate, and precise methods for determining the level of certain blood fats (cholesterol and triglyceride). This demonstrates that accurate and precise values for blood lipids can be obtained by a group of high volume laboratories. This standardization is finding wide application in many clinical chemistry laboratories in the country, thereby improving the accuracy of detection of one of the three major coronary heart disease risk factors. In July 1973, these clinics began a study to determine whether reducing blood cholesterol levels in patients with this lipid disorder can slow down or prevent the development of premature coronary heart diseases. By the end of calendar year 1974, 500 patients were under study. By January 1976, about 4,000 volunteers will be enrolled in this seven-year trial.

MULTIPLE RISK FACTOR INTERVENTION TRIAL

The purpose of the multiple risk factor intervention trial, as we have reported previously, is to determine whether or not a preventive program directed at a reduction of elevated blood lipids (cholesterol), a reduction of high blood pressure, and reduction or elimination of cigarette smoking will result in a significant reduction in deaths from

coronary heart disease. Over 150,000 men have been screened for coronary heart disease risk factors to determine their eligibility for participation in this study. From these approximately 40 percent of the enrollment goal of 12,000 men with higher than average risk of developing heart disease was achieved. Patient enrollment is expected to be completed during calendar 1975 in this 6-year research effort.

HYPERTENSION DETECTION AND FOLLOWUP PROGRAM

In 1973 another major epidemiological and community study, the hypertension detection and followup program, was started. Cross-sections of ethnic and racial groups and of socioeconomic strata in 14 communities are being studied for prevalence of all ranges of high blood pressure. The purpose of the program is to assess the ability of a program of long-term antihypertensive therapy to reduce mortality and morbidity from high blood pressure and its clinical manifestations. The past year has seen the completion of screening of approximately 160,000 persons. The goal to enroll 10,500 individuals in a controlled study has now been attained. An important component of this study relates to health education and behavioral research as these may affect adherence to therapy and personal attitude toward hypertension.

CORONARY DRUG PROJECT

We reported to you last year that the coronary drug project, a 5-year clinical trial studying the effectiveness of five different drugs in the prevention of a second heart attack in more than 8,000 men, had already shown that three of the drugs under test did not help the patient by either preventing a second heart attack nor lessening the seriousness of the second episode. We must now report that in terms of improved patient survival or reductions in risk from cardiovascular deaths, the benefits of therapy from the other two drugs were also negative. However, I would like to underscore that had this trial not been conducted, thousands of patients would continue to be treated in good faith by conscientious physicians with drugs which have now been shown not to benefit this particular category of patients. In addition the coronary drug project has demonstrated that data of high precision and reliability can be obtained through large-scale cooperative ventures involving many institutions and investigators following a common protocol. In addition to the findings with respect to the drugs evaluated, the project gained a very large body of valuable data on the natural history of coronary heart disease. Again, through the Institute's health education programs, knowledge of these findings was disseminated to the public and they have already been published in scientific literature. Now the Institute is planning a direct communication to physicians.

LIMITING HEART MUSCLE DAMAGE

During recent years experimental studies have shown that when the blood supply to heart muscle is cut off by a heart attack the amount of heart muscle irreversibly damaged can be reduced by several different techniques. Reducing the workload of the heart by the careful administration of drugs to slightly reduce the blood pressure, or by mechanical devices to assist the pumping action of the heart (the "intraaorrtic

balloon") have shown encouraging results in limited clinical studies. Several promising drugs increase blood flow to the heart muscle, some by reducing swelling, others by dilating vessels, and others yet apparently by increasing diffusion of nutrients in the tissue. On the basis of these promising laboratory and clinical studies, an expanded program for protecting jeopardized heart muscle has been launched.

As you know, our programs are not limited to heart and vascular diseases. The broadened mandate for the Institute emphasized the need to expand our efforts in lung disease and in certain blood diseases, notably sickel-cell disease and blood resources.

LUNG PROGRAMS

The Institute's former fledgling lung research programs have been expanded dramatically over the past few years into a coordinated national program. There exists a basic critical mass of research findings which, I believe, will revolutionize our future approach to the prevention and treatment of respiratory diseases.

For instance, membrane oxygenators that combine adequate gas exchange with minimal blood destruction have been developed. The principal premise for their use is, that if one can provide respiratory support and remove the threat of oxygen toxicity during the period of respiratory crisis, the lung may recover and the auxiliary oxygen support can be removed. These oxygenators have demonstrated sufficient promise to warrant intensive evaluation.

Numerous ongoing studies are concerned with the general program of developing biological methods to separate lung cells. An extensive effort is addressed to developing cell structures of homogeneous cell types to study cellular structure, metabolism, and function. This is an especially formidable task with regard to the lung, which has approximately 40 different types of cells, making it one of the most heterogeneous organs of the body.

Important in the molecular understanding of lung diseases is the role of surfactant—a pulmonary surface active ingredient. Surfactant and its alterations seem to play a functional role in a number of lung disorders, including neonatal and adult respiratory distress syndromes, oxygen, toxicity, and pulmonary edema.

There have been improved understanding of respiratory distress and respiratory failure. A primary complication of respiratory failure is a low oxygen contest in the blood, despite the presence of normal oxygen in the inhaled air (a condition called hypoxia). Because of the dire consequences of blood hypoxia, a recently developed technique for prompt and rapid identification of physiologic changes that are associated with hypoxia and the extent to which they contribute to the patient's condition, offers great promise. Although still in the developmental phase, the technique has given encouraging results at several centers and should lead to therapy that can be directed to the causes (rather than the effects) of hypoxia.

YOUNG INVESTIGATOR PULMONARY RESEARCH GRANT

The recently initiated young investigator pulmonary research grant program is intended to foster the pulmonary research interests of young scientists and physicians by providing them with modest, inde-

pendent support for a project of their own design. It is designed to encourage young investigators who are in basic science and clinical disciplines to channel their interests to pulmonary disease-related research. The first competition has to a noteworthy extent achieved these objectives. Fifty percent of the applications are from institutions that have never or only rarely received support from NHLI.

PULMONARY FACULTY TRAINING PROGRAM

The Institute has announced competition for a new national pulmonary facility training program. This program is intended to strengthen pulmonary facilities at schools of medicine and osteopathy which have not yet developed adequate programs addressing to respiratory disease. Junior faculty members from schools wishing to strengthen their pulmonary academic programs will be provided the opportunity to obtain extensive pulmonary training at medical centers with strong academic programs. After the formal training, the junior faculty will return to the school that sponsored the training, and develop a program of research, teaching, and clinical care in respiratory diseases and disorders.

BLOOD DISEASES

Turning to blood diseases, in two major hereditary blood diseases—sickle-cell anemia and Cooley's anemia—the problem resides in a specific defect in the production of hemoglobin, the oxygen-carrying red pigment of the red blood cell. In sickle-cell anemia the defect is in the hemoglobin molecule itself. In Cooley's anemia the defect is in the synthesis of hemoglobin. Now that these basic defects have been identified, scientists are seeking means to correct them.

SICKLE-CELL DISEASE

Under the sickle-cell disease program the Institute supports screening and education clinics administered by the Health Services Administration. These clinics will develop and field test new screening and counseling methodologies and programs to improve public education and patient referral under various circumstances in a variety of environments. During the past year approximately 400,000 individuals were screened for sickle-cell trait. Approximately 1 in 10, or 40,000, were found positive and were given appropriate counseling on the nature of the disorder. In addition, the comprehensive sickle-cell centers supported by Institute grants have screened over 100,000 individuals. Under the sickle-cell program substantial progress has been made in the area of diagnosis and several new agents are being investigated for their ability to prevent the painful vasco-occlusive sickle-cell crisis.

HEMOPHILIA

The hemophilias are generally transmitted bleeding disorders in which blood does not clot normally. During recent years the outlook for the hemophiliac has changed substantially as a result of significant advances in research.

Mr. Flood. Does the hemophiliac transmit under the Mendel theory more or less?

Dr. RINGLER. It is carried on the sex chromosome so it is transmitted by the carrier mother.

Mr. FLOOD. By generation?

Dr. RINGLER. Yes.

Mendel's theory is appropriate if you qualify it by saying it is carried on the sex chromosome. Improved preparations of antihemophilic factor, the missing clotting factor in these patients, are now available. Our major long-term goals are to better understand the genetic and pathologic mechanisms underlying bleeding disorders.

HEPATITIS

The reduction of the risk of posttransfusion hepatitis remains a major challenge. Recent advances in the understanding of hepatitis and its transmission must be further improved and implemented in the national practice of blood transfusion and blood banking. In one current development, trials of a high potency gamma globulin preparation used in groups at high risk are nearing completion.

These are but a few highlights of programs being carried out through the national program. I have tried to select examples which show how basic research studies are prompted by patients' needs and disease problems, how research findings are used in clinical applications, and ways in which we attempt to pass on new findings to the general public as well as the medical profession.

Mr. FLOOD. What is the nature of the binding of oxygen to hemoglobin?

Dr. RINGLER. Oxygen is bound to the hemoglobin in a type of loose binding from which it is readily released.

Mr. FLOOD. Its absence would produce what?

Dr. RINGLER. Under normal biological conditions it would not be totally absent. It would be reduced at the point where the red cells reach the capillaries.

Mr. FLOOD. Is there any way by the degree of color that you could test it, just by the shade perhaps?

Dr. RINGLER. Yes, sir.

As a matter of fact, there are tests for degree of oxygenation of hemoglobin that are based on the brightness of the red color.

BUDGET REQUEST

In conclusion, Mr. Chairman, the budget request for the National Heart and Lung Institute for 1976 is $292,794,000. I shall be pleased to answer any questions and supply additional information desired for the record.

AUTHORIZING LEGISLATION

Mr. FLOOD. Doctor, your authorizing legislation for your program, title IV, part B, and title XI, expires on June 30, 1975.

Dr. RINGLER. That is correct.

Mr. FLOOD. If this committee appropriated the money under title III, section 301, would you be able to carry out all of the activities of the Heart and Lung Institute under that title?

Dr. RINGLER. My budget officer tells me yes, except for the training.

Mr. FLOOD. Well, the answer is no then. Training is certainly one of the activities, so your answer is no.

Mr. MILLER. Excuse me. I think the problem on training does not relate to the special heart legislation. It relates to the expiration in fiscal year 1975 of the general training authority for NIH.

Mr. FLOOD. Anyhow, if the answer would be no, in spite of what Mr. Miller just said, what activities would you be able to carry out in that way under that section?

Dr. RINGLER. All of the sections of that authority provide for the support of all of our research programs. They provide the authorization for training exclusive of reseach training and they provide several special authorizations.

Mr. FLOOD. Has the Department submitted a legislative request to extend the authorities of title IV and title XI?

Dr. RINGLER. No; the Department has not submitted a request.

IMPACT OF 1976 BUDGET REDUCTION

Mr. FLOOD. Your budget proposes a reduction of $32,346,000. What is the overall impact of that reduction?

Dr. RINGLER. The reduction comes down to approximately $15 million in the grant line and about $17 million in the contract line. What we will do is examine our programs and will necessarily have to readjust priorities.

Mr. FLOOD. Realine them.

Dr. RINGLER. Realine priorities in order to accommodate that change in funding availability.

Mr. FLOOD. In your justification material there you state under this budget, and let me quote:

"Moral commitments of lower priority, noncompeting grants, will not be funded."

How do you go about deciding what is a low-priority project?

Dr. RINGLER. This would be done on a project-by-project, program-by-program evaluation and in the last analysis it would be made on the basis of a judgment as to which aspects of the program are more important.

Obviously that cut is such that a reduction in the order of about 10 percent has to be achieved in order to bring it about.

Mr. FLOOD. How much money do you need in fiscal 1976 to fund these noncompeting grants?

Dr. RINGLER. About $15 million.

Mr. FLOOD. Doctor, if we were to restore your budget to the 1975 level, how many new research grants would you be able to award?

Dr. RINGLER. I think on the order of about 200.

Mr. FLOOD. Would you use all of these restored funds only for new grants?

Dr. RINGLER. You would use them for new grants and contracts and for grants that——

Mr. FLOOD. They wouldn't all be used then for new grants, or would they, or what?

Dr. RINGLER. If funds are to be restored some of them would be used for new grants.

Mr. FLOOD. You could change an old one so much it could be new, I guess. Is that it?

Dr. RINGLER. I was going to say that we would probably provide support for continuation of some of the old grants that may not have otherwise been continued.

REDUCTION IN DEATH RATES FROM CORONARY HEART DISEASE

Mr. FLOOD. A couple of days ago—I guess you weren't here—Dr. Cooper testified before us and he indicated there was a 10-percent reduction in the death rate from coronary heart disease. Do you want to comment on that and tell us how your work at the Heart and Lung Institute has contributed to that reduction?

Dr. RINGLER. There has been a reduction in the death rate from heart attacks or coronary heart disease of about 2 percent per year beginning with 1969. This is following a period when, as you are well aware, heart attacks were increasing very dramatically during the fifties and sixties and then around 1965 the increase began to level off and finally around 1968 or 1969 it began to decline.

So Dr. Cooper is saying there has been about an 11 percent decline thus far. What has contributed to that? Probably a great many factors. I tried to point out some of them in my opening statement.

They relate to a better understanding of the risk factors for heart disease, the major ones being smoking, elevated lipids, hypertension, probably better attention and better treatment of high blood pressure, better diagnostic and better treatment methodologies.

I mentioned in the statement that we have had a myocardial infarction research units program. I think they have made substantial contributions in terms of improved treatment, improved diagnosis, following a heart attack.

CIGARETTE SMOKING

Mr. FLOOD. Are you favoring this proposal to put either the word "kill" or the word "death" on cigarette packages?

Dr. RINGLER. I personally would feel that there should be a strong statement against smoking.

Mr. FLOOD. Can you go further than kill or death?

Dr. RINGLER. I wouldn't necessarily want to endorse each of those words.

Mr. FLOOD. That is what I asked you. What is your thinking? If you say "kill" or "death" you are going pretty far, aren't you?

Dr. RINGLER. There is pretty good evidence that you shouldn't smoke.

HEART COOPERATIVE DRUG STUDY

Mr. FLOOD. That will be the understatement of this afternoon.

Also in your budget justification—we read these things, you know; I don't know who writes them but we read them—you are phasing out the heart cooperative drug study. Is it reaching the point of completion or is it being phased out because of lack of funds or what?

Dr. RINGLER. It is being phased out because it is over. It is finished. We have been promising you for years that we were going to bring that study to conclusion and publish the reports.

Mr. FLOOD. And I have asked it every year.

Dr. RINGLER. Yes, and this year we not only phased it out but published the basic data. The last patients were seen in February.

RESEARCH AND DEVELOPMENT CONTRACTS

Mr. FLOOD. On page 80 of your justification you state you are supporting targeted research and development contracts.

How much money are you investing in targeted research and what are some of the projects you are supporting with the contract mechanism?

Dr. RINGLER. The contract approach is used when we want to emphasize some specific problem. The Institute's budget for contracts is approximately about $64 million for 1976. That includes a wide variety of activities.

It includes, for example, the lipid research clinics that I mentioned a few moments ago. It includes work on sudden cardiac death. It includes our program on medical devices and circulatory assist devices. I am trying to give examples from the Institute as a whole.

It includes programs in the area of lung disease. It includes targeted programs in blood banking. It covers the spectrum of the Institute's activity.

DEVELOPMENT OF DIAGNOSTIC AND TREATMENT TECHNIQUES

Mr. FLOOD. Doing the same kind of thing, can you identify for the committee the diagnostic and treatment techniques that your institute has developed, let us say over the last couple of years, the last 2 years, which now are routinely being used by practicing physicians?

Dr. RINGLER. I can give you an answer to that question here. I can give you a fuller one for the record, either way you want to do it.

The devices that have been developed by the Institute in recent years include, for example, the so-called intraaortic balloon which is being used now for a variety of conditions, among them treatment of cardiogenic shock.

Mr. FLOOD. I see what you mean. Develop that for the record because we want that especially for the record.

Dr. RINGLER. I would very much like to develop that for the record.

[The information follows:]

DIAGNOSTIC AND TREATMENT TECHNIQUES NOW IN ROUTINE USE HEART AND VASCULAR DISEASES

Among the diagnostic techniques that have come into much greater use in the past 2 or 3 years are the use of ultrasonic methods for detecting and diagnosing lesions of the heart. This means that often a cardiac catheterization which requires the threading of a tube into the heart and X-rays of the heart requiring injection of contrast medium into the blood inside the heart can be eliminated, and a good picture can be obtained of the important characteristics of the heart. This technique is in increasingly wide use in adults, and it is particularly of importance in infarcts where the cardiac catheterization is difficult and the urgency of diagnosis is great.

Some of the other diagnostic and evaluative techniques which have come into substantially greater use have been methods for more precisely detecting the presence of a heart attack and for quantifying the severity of it in terms of muscle damage. Techniques utilizing the blood levels of enzymes liberated from injured heart muscle is one approach. Another deals with mapping the electrical activity of the heart as it appears at multiple sites on the surface of the chest. Neither of these techniques is fully proven, but they are serving as good first indicators of the extent of heart damage until we have better techniques.

Among the therapeutic modalities in much more extensive use over the past 2 or 3 years is the intra-aortic ballon. By this technique the pressure in the arterial system is artificially elevated in a circumstance where the heart and

appropriate drugs are unable to maintain blood pressure at its normal level. The device consists of a distensible balloon at the end of a catheter which is threaded from the groin into the artery which goes towards the main artery coming from the heart, the aorta. The balloon is made to expand and contract synchronously so that during its collapse it diminishes the pressure seen by the contracting heart and, therefore, diminishes its workload; as the balloon expands, it increases the pressure in the arterial system. The technique is finding increasing use in the short-term treatment of some forms of cardiogenic shock, particularly for tiding patients over until diagnostic evaluation such as coronary angiography and definitive therapy such as reconstructive coronary bypass surgery can be performed.

Another therapeutic technique of increasingly wide use in the past year or two is the careful adjustment of the blood pressure of patients who have had a heart attack to slightly lower it—sufficiently slightly to diminish the workload of the heart but not so much as to diminish the perfusion of the heart or the vital organs. The precise balancing of this requires considerable care, and the exact techniques and drugs utilized are still being worked out.

Lung Diseases

DIAGNOSIS

Recently, fundamental research in physiology, biochemistry, and immunology has been able to be applied to diagnosis because there is now a better recognition of the pathophysiology underlying disease. Noteworthy accomplishments relate to respiratory distress syndrome, allergic disorder and hypoxia.

a. Prenatal diagnosis of respiratory distress syndrome

Because untreated neonatal respiratory distress syndrome has such a rapid down-hill course, research on accurate early diagnosis has elicited a high level of interest. Investigators are capitalizing on the findings of fundamental research, especially with regard to the formation and physical and chemical characterization of the surface-active material—surfactant. Especially significant are tests that predict the degree of lung maturation from analysis of amniotic fluid. Two lines of research have contributed greatly to validation of these prenatal tests:

Recent work has confirmed earlier observations that the lecithin to sphingomyelin ratio (L/S) is abnormal in cases of lung immaturity.

Recent studies have definitely established the presence of specific proteins in the surface-active material. Moreover, these proteins have been isolated in soluble form and can be utilized for quantitative immunologic assay of surface-active material in human amniotic fluid. Figures for the level of surfactant apoprotein correlate well with L/S ratio data and this assay appears to be a good predictor of the risk of respiratory distress syndrome in the newborn.

b. Diagnosis of allergic diseases

Renewed interest in the challenge technique is providing a sound pathophysiologic basis for improved diagnosis of allergic diseases. The challenge test utilizes inhaled compounds that cause a bronchial or alveolar immunolgic response. Until recently, patients were challenged with unspecific compounds such as methacholine. But now specific antigens are used, permitting observations that have led to better understanding of the disease mechanisms in asthma and hypersensitivity pneumonitis.

TREATMENT

Treatment of many respiratory diseases is addressed primarily to alleviation of symptoms rather than to their cause. This tends to correct the failure in respiratory function without regard to whether it is a primary disorder or is secondary to other aspects of lung dysfunction.

Recent accomplishments have made significant contributions to correcting or sustaining respiratory function in acute respiratory distress.

a. Continuous positive airway pressure

Continuous positive airway pressure has for some time been used with notable success to treat neonatal respiratory distress syndrome, but, until recently, the technique could only be effectively applied in centers where sophisticated technology and specially trained staff were available.

Several laboratories have recognized the potential danger of the effect of elevated airways pressure on the cardiovascular system, and in recent studies they have refined the indications for use of positive airway pressure and established its limitations. As a consequence of these studies, the technique can now be safely used even in small hospitals or hospitals distant from large academic centers. Thus, the improved survival rates achieved by academic centers can now be anticipated in many more communities.

b. Extracorporeal membrane oxygenation

Therapy of adult respiratory distress has concentrated on correction of ventilatory derangements and hypoxemia. The therapeutic techniques (volume respirator, large tidal volume, positive end-expiratory pressure and careful attention to inspired oxygen concentration) are designed to correct physiologic derangements that are now relatively well understood. In many cases, however, in spite of the extensive ventilatory support together with other clinical management, the hypoxemia worsens and death ensues. Recent research suggests that extended use of high concentrations of oxygen in ventilatory support may itself result in lung abnormalities.

Membrane oxygenators have been extensively investigated and during the last 10 years a new generation of compact, disposable models that combine adequate gas exchange with minimal hematologic destruction have been developed. The principal premise for their use in the therapeutic armamentarium for acute respiratory failure is that is one can provide respiratory support and remove the threat of oxygen toxicity during the period of respiratory crisis, the lung may recover, and the auxiliary oxygen support can be removed.

BLOOD DISEASES

Fibrinogen is a circulating protein which is converted into fibrin. This is the major component of a blood clot. Fribrinogen can be labeled with a radioisotope and its deposition in a thrombus detected. This technique permits early detection of deep vein thrombosis (thrombophlebitis) and has led to discovery of preventive therapy.

Patients with fractured hips sustain a large number of thromobembolic complications. Clinical studies with anticoagulant drugs have demonstrated their effectiveness in decreasing the incidence of such complications. This approach can be recommended for general use in such patients.

Concentrates of coagulation factors used to treat a type of hemophilia (Christmas disease) sometimes caused thrombotic problems. Basic understanding of the coagulation system allowed a systematic approach to this problem, coordinated by NHLI and the Bureau of Biologics. The manufacturers of these products will modify them in line with recommendations from these agencies.

Over the past 10 years a number of independent laboratories, supported by NHLI grant funds, have developed and defined two basic techniques for studying factor VIII, the clotting factor which is functionally absent in the hemophiliac. One method detects the activity of factor VIII as measured by a blood clotting test. A second technique distinguishes the amount of factor VIII protein by standard antigen/antibody immunologic techniques. Since all the factor VIII protein does not function, there is generally more protein then activity measurable.

The ratio of protein to activity has been suggested as an index of the hemophilia carrier. The Institute has recently conducted a workshop to determine the practical importance of this test. Preliminary results suggest that the technique, though difficult and sophisticated, will be of real value in identifying the carrier. Work in progress now should define the accuracy of the test and demonstrate the best statistical approach. Establishment of reference detection laboratories will be a practical result of these studies.

EDUCATION PROGRAMS

Mr. FLOOD. An important part of your program is consumer health education. Just a few days ago sitting right where you are we had the Center for Disease Control people up here and they told us that they were the focus for coordinating all these major consumer health education programs for the whole Federal Government.

How do you work with these people at the Center for Disease Control on the matter of health education?

Dr. RINGLER. We try to work with them very closely, as a matter of fact. There are certain activities where the focus is a very categorical one—by that I mean it is limited to one aspect of one disease—we tend to do it until we develop a methodology for health education.

The thinking is that once the methodology is perfected the CDC would attempt to bring it into a larger system. Our staff know their staff there very well and our exchange with them is excellent.

Another specific example is in the sickle cell program where they are actually carrying on specific programs in very close collaboration with us, and where NHLI provides $300,000 to CDC to help support this effort.

DIET AND HEART DISEASE

Mr. FLOOD. We hear a lot all the time about the relationship of diet to heart disease. We hear that all the time.

What are you doing in that area?

Dr. RINGLER. We have what we call the multi-risk factor intervention trial. It attempts to intervene on the three major heart disease risk factors; namely, elevated cholesterol, elevated blood pressure, and smoking. That elevated cholesterol part of it is controlled by having the subjects in the trial on a diet that reduces their cholesterol.

Mr. FLOOD. As part of your education program in that area, are your promoting a more healthful diet?

Dr. RINGLER. Our approach in the area of diet is one that we would refer to as prudent. The position would be that for most of us the problem is that we eat too many calories. So rather than promote a diet that has a certain content of a specific food substance we have tried to propose a diet that bears some relationship to the needed caloric intake.

AUTHORIZING LEGISLATION

Mr. FLOOD. By the way—I asked you before and I wasn't clear about that—can you carry out all those activities that I mentioned that you are talking about in the budget under the authority of that section 301, all of them?

I thought you said yes, didn't you?

Dr. RINGLER. The answer is "Yes."

Mr. FLOOD. What can't you carry out under 301?

Dr. RINGLER. We can't carry out the control programs and we cannot carry out research training.

DIABETES

Mr. FLOOD. When Dr. Cooper was here on Monday he said that 75 percent of all diabetics die from heart disease. As you know, the Diabetic Act requires each Institute to set aside a part of its budget to do this diabetic research.

What are you doing about that in your shop?

Dr. RINGLER. Our expenditure in the diabetes area now is in the order of $5 million.

Mr. FLOOD. Then you are aware of the requirement of that act?

Dr. RINGLER. The Diabetes Act, I am aware of it. There is a Diabetes Commission. I am a member of it.

NIH MANAGEMENT FUND

Mr. FLOOD. All through this budget all we see are decreases, decreases, decreases. If you take a look at page 65, there we see an $858,000 increase for NIH management fund. How do you explain that particular increase? Here you are reducing research, grants, contracts, the whole thing. Up you go on this one.

Mr. SCHWARTZ. I think perhaps I should answer that question.

The management fund, as you know, is a centrally controlled fund based upon services that are more efficiently performed by central units.

Mr. FLOOD. Yes.

Mr. SCHWARTZ. We then give the assessment to the Heart and Lung Institute based upon their expected usage of the service. The costs of the management fund have gone up as you might expect in any fund that includes a very large input of personnel services. There are actually no program growth increments in the management fund but merely the increased cost of salaries and a major increase in utility costs.

Mr. FLOOD. I want the record to show that. You may want to develop that one for the record, too.

Mr. SCHWARTZ. Yes, sir, we would be glad to.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH MANAGEMENT FUND ASSESSMENT

The Management Fund of the National Institutes of Health was created to finance certain common research-supporting services and administrative activities which are required in the operations of the National Institutes of Health. The actual cost of these services and activities cannot be readliy distributed as charges to the Institutes. The authority for the Management Fund was provided as a part of the Department of Health, Education, and Welfare Appropriation Act of 1958 "for the purpose of facilitating the economical and efficient conduct of operations in the National Institutes of Health which are financed by two or more appropriations which the costs of operation are not readily susceptible of distribution as charged to such appropriations." The organizations supported by the Management Fund have no appropriation. Thus, the costs are incorporated into the various National Institutes of Health appropriations and are associated with the several activities that contribute to the Institutes' total programs.

The authority permits a distribution of the charges to the Institutes in a fashion considered "reasonable" by the Director, National Institutes of Health. It does not require that assessment/reimbursements be related from a cost accounting standpoint to services received. The General Accounting Office agrees with the concept of the "formula" as it is applied to the Institutes and Divisions. The "formula" prorates the amounts to be distributed on the basis of such factors as the number of budgeted positions, direct research dollars, Clinical Center bed assignments, and the amount of research grant and fellowship funds that are included in each institute appropriation. The objective in the development of the formulas has been to keep them as simple as possible but yet reflect a reasonably accurate and equitable distribution of amounts.

NIH Management Fund:

1975	$85,558,000
1976	90,126,000
Change	+4,568,000

Mandatory increases for pay costs:

(GS, $1,610,000; Wage Board, $1,977,000)	$+3,587,000
Annualization of NCI laminar flow unit	+261,000
Annualization of NICHD perinatal branch	+720,000

DISTRIBUTION BY APPROPRIATION BASED ON EXPECTED USAGE OF SERVICES

Appropriation	1975	1976	Change
National Cancer Institute	$19,148,000	$20,757,000	+$1,609,000
National Heart and Lung Institute	12,711,000	13,569,000	+858,000
National Institute of Dental Research	2,589,000	2,429,000	−160,000
National Institute of Arthritis, Metabolism, and Digestive Diseases	9,962,000	9,901,000	−61,000
National Institute of Neurological and Communicative Disorders and Stroke	7,476,000	7,612,000	+136,000
National Institute of Allergy and Infectious Diseases	8,843,000	8,952,000	+109,000
National Institute of General Medical Sciences	1,905,000	1,773,000	−132,000
National Institute of Child Health and Human Development	4,348,000	5,594,000	+1,246,000
National Institute on Aging	798,000	777,000	−21,000
National Eye Institute	2,827,000	2,950,000	+123,000
National Institute of Environmental Health Sciences	851,000	834,000	−17,000
Research Resources	353,000	334,000	−19,000
Fogarty International Center	261,000	244,000	−17,000
National Library of Medicine	1,755,000	1,696,000	−59,000
Office of the Director	1,966,000	2,445,000	+479,000
Bureau of Health Resources Development	1,442,000	1,448,000	+6,000
Food and Drug Administration	947,000	1,053,000	+106,000
National Institute of Mental Health	7,376,000	7,758,000	+382,000
Total	85,558,000	90,126,000	+4,568,000

Mr. FLOOD. Doctor, can you describe your efforts in the matter of sickle-cell anemia research?

Dr. RINGLER. Yes, sir. The Institute coordinates the sickle-cell disease program for the Federal Government. We have an individual within the Institute named Dr. Rudy Jackson who is the program manager. Briefly, the program consists of a substantial effort in the area of research on trying to understand the basic mechanisms of the sickle-cell process, coupled with a large effort in prevention, control, and education.

We have several projects underway attempting to identify agents that will prevent sickle-cell crises. Persons who have sickle-cell anemia experience vaso-occlusive crises.

The complementary efforts of physicians and public education, in screening and counseling, seek to assure that these patients benefit as soon as possible from the results of this research.

Mr. FLOOD. Mr. Roybal.

DISSEMINATION OF INFORMATION—DEVELOPMENT OF EDUCATION PROGRAMS

Mr. ROYBAL. I would like to review with you briefly, but I hope not too briefly, the various media communications that you use to disseminate knowledge to the general public. I am interested in your health education technique, how you actually reach the communities. I want to know whether it is done through existing local agencies, or whether or not you have health educators that you assign to various communities to do the work. Could you elaborate on that?

Dr. RINGLER. Let me begin by saying that this is a new activity for us, and we are trying various approaches to the whole area of public education. We do not have people within the Institute that we can assign to individual communities.

What we do have in the Institute are people who might be described as health educators who help us, with other groups, develop educational materials. To go on to your question, regarding media that we use, we attempt to use all media. For example, we used quite a large

number of TV spots last year to carry various health messages. The vast majority of them have been in the high blood pressure area.

We have used magazines and periodicals. There have been a large number of spots on the radio.

What is more, we develop packages that we can send out to a community. We have sent some to communities in your area, for example, that hopefully could be adapted to fit a local situation. They are developed in a way that they are intended to be keyed, if you will, to the specific population group.

Some of the materials are developed in Spanish as well as in English.

Mr. ROYBAL. How much of this material is actually developed in Spanish? For example, do you have any Spanish leaflets?

Dr. RINGLER. Yes, sir; in the hypertension area.

Mr. ROYBAL. Or other health education paraphernalia in the Spanish language?

Dr. RINGLER. Yes; in the hypertension program we do.

Mr. ROYBAL. What about tuberculosis? TB is increasing throughout the country. Do you also have something in the Spanish language?

Dr. RINGLER. No. The TB program at NIH comes under the purview of the National Institute for Allergy and Infectious Diseases.

Dr. LAMONT-HAVERS. That is primarily for the development of new knowledge. The development of the community type of programs in tuberculosis would primarily be the responsibility of the Center for Disease Control which testified on Tuesday and possibly, to some extent, of the Health Services Administration.

The type of programs in tuberculosis which NIH does is primarily to develop information concerning the organism itself or the means of overcoming it.

Dr. Davis, the Director of the Allergy Institute, has that responsibility.

You are quite right, there are some atypical forms of TB which are now developing in this country.

ROLE OF NHLI IN THE DEVELOPMENT OF EXPERIMENTAL APPROACHES TO EDUCATION

Mr. ROYBAL. Yes, but with reference to the techniques of reaching the public, whether it be hypertension, TB, or anything else, do they originate from your office so that the same technique and the same approach is used throughout the Nation?

Dr. RINGLER. I would answer that by saying some of them do originate from our office, when they relate to an experimental approach, if you will, to public education. My understanding is that the Center for Disease Control will be the focal point for health education within the Department.

Dr. LAMONT-HAVERS. At NIH there are really only two Institutes which have permission to do demonstration and control programs. Those are the National Cancer Institute and the National Heart and Lung Institute. The Heart and Lung Institute programs are primarily in hypertension and sickle cell anemia.

The other Institutes do not have that kind of activity as part of their mission.

Mr. ROYBAL. It seems to me that demonstration programs have already been in existence, since before 1940 when I first went into that field. We were supposed to demonstrate to the official agencies then that certain techniques could be successful in disseminating information to the community and consequently resulting in lowering the rate of disease in that particular sector of the area in which we operated.

How long are we going to continue to demonstrate and what are we doing to actually get the communities as well as the medical profession involved. At the time that I started in this field I spent the first 8 months of my employment debating the subject: "Is Mass Radiology Socialized Medicine?" My opponents were doctors from the American Medical Association and the California Medical Association.

They, at that time, were saying, "Yes, it is socialized medicine and this is going to ruin the so-called doctor/patient relationship."

I remember also conducting the first program in the State of California back in 1942 that we called a multifacet program, I think it was.

Dr. RINGLER. Multiphasic program.

Mr. ROYBAL. Thank you. Multiphasic program, where we, besides chest X-rays, also conducted blood tests, urinalysis, and other things. By that time it was no longer called socialistic. We were accused of going to far and some said it could very well be called Communist.

Do we have that problem today, or is that no longer a problem?

Dr. RINGLER. I would answer that, at least in my experience, with an emphatic no. For example, in our high blood pressure program we use the word "coordinated." It is coordinated by the Heart and Lung Institute but the program involves the participation of the major medical societies. It involves such organizations as the American Heart Association and a large number of organizations in terms of planning and execution of the program.

So I don't think that is a problem, at least not in my experience.

The other point that you make, do we continue to demonstrate forever, the problem there in my judgment is somewhat more complicated. An example to illustrate it would be, again in hypertension, it is pretty well documented that if people's blood pressure is elevated it should be treated.

The problem is to motivate people to have their blood pressure checked on a routine basis and if it is found to be elevated to somehow motivate them to stay on the medication they need to take in order to keep it down.

Ordinarily, people who have high blood pressure don't experience any ill effect. In a word, they don't feel sick. Hence, they don't really see why they should go and have their blood pressure checked and why they should take those pills that sometimes makes them feel worse than they did before they took them.

So it is a problem of adherence. When we say we are trying to motivate patients to take medication to treat high blood pressure, in my example, we are trying to learn how to do that. We are trying to find out what are the characteristics of people who do, in fact, stay on their medications and those who take them for a week or month and then stop.

Those are the kinds of things that we are trying to emphasize within the Institute.

HEALTH EDUCATION AT SCHOOL LEVEL

Mr. ROYBAL. Wouldn't it be profitable to start the program early at the school level so that by the time they get to an age where this is liable to happen they were already pretty well versed as to what the effects would be and how important it is that they take these examinations?

Dr. RINGLER. I think, again, the answer is yes.

Mr. ROYBAL. What is being done to actually get it to the school level?

Dr. RINGLER. We have several programs going on now where we are attempting to introduce that type of health education in the school level. For example, in a city in the Southwest we are attempting to get baseline information about the youngsters' health habits, health practices, and we will then undertake a program of health education to motivate them—for example, how many of them smoke and how many of them can you motivate to stop smoking.

COORDINATED MODEL PROGRAM FOR HEALTH EDUCATION TECHNIQUES

Mr. ROYBAL. Is there one particular program in some city somewhere that one can examine that you may classify as the model with regard to health education techniques?

Dr. RINGLER. I would have to think about the answer to that. If I had to pick a single city for the whole country I can think of several cities that stand out in one area or another, if you will, but to pick one that is the model for the whole Nation, I am reluctant to do that.

In certain parts of the country, for example, they have a totally voluntary blood banking system where the blood is donated and the blood supply is very good. Again to go back to the schools, in that community they have sought donor recruitment in the schools and the idea is to start a practice of blood donation while still in high school.

Mr. ROYBAL. What I would like to see is a coordinated program which your Institute and the various unofficial and official agencies coordinate in the delivery of health education paraphernalia and also the use of direct contact between the health educator and the students themselves as has been done in the past, with the old tuberculin test that was used in schools.

This was a direct contact with the health educator. The nurses and the doctors were involved, where the community actually participated in these programs, and it became not a program of the school but a program of the community.

This kind of program, I would say, would be a model program and that is what I was seeking, information with regard to a particular program that may be in existence at the present time somewhere in the United States.

Is there any such thing?

Dr. RINGLER. There are many programs of the kind that you describe that I think are very good. They are in the areas that I have

mentioned. I am reluctant to identify one that is a model for the whole country because I don't know about several of them. I think the kind of thing that you are talking about is very desirable. In the hypertension area and in the sickle cell area, in both cases, we have tried to assist communities in developing model programs, if you will, for those areas.

We have not gotten to the point where we can bring this into a total model program for disease control across the board.

Mr. ROYBAL. In other words, we are still in the stage of demonstration and not the actual delivery of the health system.

Dr. RINGLER. We are in the area of demonstration, to refer back to my earlier example, of trying to demonstrate how you get people to take their medications for, for example, elevated blood pressure. Until we know how to do that——

Mr. ROYBAL. I still come back to my previous question: How long are you going to demonstrate?

Dr. RINGLER. Until we learn how to do it.

Dr. LAMONT-HAVERS. To answer your question, sir, I think we can put something in the record after conferring with CDC and the Health Services Administration.

They have more of the responsibility for taking in community programs, getting things started, and making sure that both the State and local health communities undertake those responsibilities. Certainly, in the vaccine area this has been well tried out. I think it might be well if we try to coordinate our answer with both those agencies.

Mr. ROYBAL. I am asking these questions because in my recent travels throughout my own State I did not find anyone who would admit that such a program was in effect. In fact, it was just to the contrary, that everything that had been done was really not designed to involve the community or the parent.

It seems to me that if we are going to continue to try to teach old dogs new tricks, that we are not going to get Fido to respond, while if we direct our health education to the schools, we will find that in a few years these people will be much better educated with regard to health facilities than we are today and probably much better health educated than those who came before us.

So, it seems to me that we are wasting a lot of money when we do not direct such a program to the segment of the population that can best take advantage of it.

Now there are a good many of us, for example, who are supposed to see a doctor once a year. I will bet almost anything that not even the doctors have a complete physical examination once a year. They are too busy.

That is one of the big mistakes that is made. I try to go every year because this has been pounded in my head for years, but it is not every year that I go on the year. Sometimes I am as much as 2 months late. That is too much. Still here I sit and preach all of this, but I don't practice what I preach. How can we expect individuals who have not had exposure of this kind to respond? If you get them early, I think it can be done.

I hope a program like that can be designed, if it has not been, and then actually put into effect.

Dr. RINGLER. We would like to assist in the part of it that falls within our area. The point you are making I think is a very valid one.

In fact this is the aim of our sickle cell disease clinics and education programs which we coordinate and support through HSA and CDC.

Mr. ROYBAL. I am going to speak to a convention of the health educators soon. I am going to try to make that point to see if there can be a system of coordination that at least in my opinion does not exist today. Who knows, someone may take it up and something may happen.

PARAPROFESSIONAL PERSONNEL

Now, there is another thing that kind of bothers me. You say on page 3 of your testimony, you mention nonprofessional personnel. What does nonprofessional personnel mean?

Dr. RINGLER. I noticed that when I was reading it. As is is used here it means nonphysicians. It is a poor choice of words. I think that is probably your point.

Mr. ROYBAL. Would you like, then, to have that taken out of the record and reworded?

Dr. RINGLER. The words that I would normally use myself are "allied health personnel."

Mr. ROYBAL. That could be anyone with training in the field?

Dr. RINGLER. Yes.

Mr. ROYBAL. And thye are still a professional.

Dr. RINGLER. Yes.

If you were here when I read that, I noticed it but it slipped by, in all honesty.

DEVELOPMENT OF PULMONARY RESEARCH PERSONNEL

Mr. ROYBAL. On page 9 your emphasis seems to be on the education in medical schools in the area of pulmonary disease. Do you propose the training of allied medical personnel as well?

Dr. RINGLER. Not under our program at this time. The lung and respiratory disease program came to our Institute in 1969.

Since our main thrust is in the research area, the emphasis is to build up a pool of investigators who know something about respiratory diseases and are able to undertake a research program in that area.

So the thrust of this is to develop research scientists. We do not ordinarily provide training for the allied health personnel as I suspect you are referring to.

PULMONARY DISEASE CONTROL PROGRAMS

Mr. ROYBAL. All in all, how much is being spent for pulmonary disease control?

Dr. RINGLER. Within our Institute, it is in the order of half a million dollars.

Mr. ROYBAL. Is any particular program anyplace in the Nation being curtailed?

Dr. RINGLER. I would answer that by saying that again, we have attempted to place our greatest emphasis on developing the research aspect of the pulmonary program and that we have at this juncture not attempted to place as great an emphasis on the control part of the program.

I just said that we have a half million in the control program. That is true. We do have a major effort that is part of one of our centers that would qualify as a control program. The reason I did not include it in the answer is because technically the bookkeeping is not under the control program.

LEVEL OF FUNDING IN LUNG PROGRAMS

Mr. ROYBAL. The concern some people have expressed with regard to the curtailment of the programs may have some truth to it, then.

Dr. RINGLER. The lung program in our Institute in 1969 was on the order of $9 million.

Mr. ROYBAL. Are you increasing it for this year or is it being decreased?

Dr. RINGLER. In 1976 it will be in the order of $40 million for grants and contracts.

Mr. ROYBAL. So it started in with $9 million and now it is up to $40 million.

Dr. RINGLER. Yes, sir.

Mr. ROYBAL. Then the individuals who have contacted me with regard to expressing their fear that they will not be getting their funds at the right time and for the purposes originally intended, do not really have anything to fear.

Dr. RINGLER. I would say the funding for the lung program, relatively speaking, is good.

Mr. ROYBAL. Does that mean that it is going to be funded at least at the level that it had last year or perhaps increased?

Dr. RINGLER. At this budget, it will have to be funded at somewhat less than last year.

Mr. ROYBAL. That is what I was getting at.

Dr. RINGLER. In the narrative it says we will have to examine our program, and we will have to curtail programs of lesser emphasis or priority.

Mr. ROYBAL. If it is going to be funded at a level less than last year, then it is not that good, is it?

Dr. RINGLER. That is why I used the word "relatively." Relative to the other programs. They are all going to be cut back some.

Mr. ROYBAL. I thought you were playing with words.

I appreciate the fact that you have to, to some extent, but what I wanted to get at is whether or not there is less budgeted this year than there was for last year, and your answer is yes.

Dr. RINGLER. Yes, sir.

Mr. MILLER. Can we make sure we get our years straight? There was more money in the original President's budget for fiscal 1975 than for 1974. But then, of course, the appropriation for 1975 was much higher, and the rescissions were turned down. So 1976 will be lower than 1975 which is next year, not this year.

ATTITUDE OF EMPLOYERS TO EMPLOYEES

Mr. ROYBAL. Yes; I understand that.

Now, we have talked a little about chart pathology. Do you propose to utilize funds to study the aftermath of heart and lung disease, particularly the attitude of employers toward employees?

I remember that that was once a problem. Those who had had, for example, active tuberculosis and went to a sanitarium and ended up with an arrested case, were nevertheless stigmatized. The employers didn't want them back; and new employers, once they saw that they had spent time in a sanitarium, didn't want them in their employ. Is that a problem today?

Dr. RINGLER. That is not an area of major activity in our Institute, but we do have some activity in the area. What you point out is a problem for the hemophiliac, for example.

Also, following a heart attack, individuals frequently have difficulty finding reemployment. We are in the process now of trying to get some measure of the dimensions of that problem, to find out what the physician's attitude is about patients going back to work following a heart attack, and also to get some sense of employer and patient attitudes in the area. As I said before, it is not a major activity of the institute, but it is a part of a total program on heart disease because the goal is to rehabilitate people so that they can go back to work. To a lesser degree, it is also a problem in lung disease. We are working with a committee that is made up of labor, management, and medical people who are attempting to identify, if you will, the dimensions of the problem. I think in the example that you cited, tuberculosis, it was a somewhat different problem because of the communication of the disease.

Mr. ROYBAL. Because of the increasing instance of tuberculosis, I feel perhaps it may become a problem.

Dr. RINGLER. Perhaps so.

Mr. ROYBAL. Again, this is probably based on lack of information on the part of the employer.

But there is still that tremendous fear, you see, a fear that existed in the Middle Ages, and back in historical times more than anything else. But nevertheless, there is genuine fear on the part of an employer that a person may contaminate all the rest of his help.

Well, it may be a problem that these various techniques in health education that we were talking about may eventually take care of.

It may take some time.

SICKLE CELL ANEMIA

Mr. STOKES. Dr. Ringler, for my first question, if you would like, you can just furnish this for the record. I don't have to have it at this time.

I would like for you to put into the record at this point exactly what sickle cell disease is.

I would like to have you describe its characteristics, the incidence of the disease in blacks, the number of persons who are affected, the rate of death, the number of persons who are living with the disease, and a full and complete discussion, if you will, of sickle cell anemia disease.

Would you do that?

Dr. RINGLER. Yes, sir, we will be glad to do it.

[The information follows:]

DESCRIPTION OF SICKLE CELL DISEASE, ITS CHARACTERISTICS, INCIDENCE, MORTALITY, ETC.

Sickle cell trait, the most common inherited blood abnormality in the United States, is believed to be carried by more than 2 million U.S. citizens, primarily blacks. However, most of these carriers are healthy. If two carriers marry, each of their children has a 1 in 4 chance of having sickle cell anemia, a painful and debilitating disorder affecting nearly 50,000 individuals. About 1 in 500 black babies in this country is born with sickle cell anemia.

Sickle cell anemia is a disorder characterized by the presence of painful crises which may last for hours or days, a chronic anemia related to accelerated destruction of red blood cells, and acute and chronic damage to various body organs. These clinical manifestations are caused by the presence of an abnormal hemoglobin, Hb S, leading to crescent shaped sickled red cells. Sickled red cells have difficulty traversing the small blood vessels and tend to occlude them. This in turn results in impaired circulation, tissue damage, and painful crises.

Sickle cell anemia, the homozygous state for the gene for Hb S, S/S disease, often causes severe and disabling symptoms and may markedly shorten life. Milder symptoms and greater longevity are encountered in certain genetic variants of sickle cell disease, Hb S-thalassemia.

If sickling of the red cells could be altered or prevented, perhaps by a suitably designed pharmacological agent, both the quality and duration of life for patients with sickle cell disease would be greatly improved. While we know the primary defect in sickle cell disease—a mutation which leads to the substitution of a single amino acid in one of the two kinds of polypeptide chains in hemoglobin—much remains to be learned about the formation and structure of the aggregates of deoxygenated Hb S and the interactions of these polymers of Hb S with other red cell components. In a sense, the molecular and cellular manifestations can be considered causes of sickle cell disease, since the clinical manifestations are based upon the molecular and cellular phenomena.

The cost of caring for a patient with sickle cell disease may approach $2,500 to $5,000 a year. The loss of time from school and jobs, and the resultant psychological and educational problems, make this disorder one of high social and economic impact.

Mr. STOKES. We are talking about a disease here that we still have found no cure for, is that correct?

Dr. RINGLER. That is correct.

INTRADEPARTMENTAL COORDINATION

Mr. STOKES. Can you give me some idea of what the interaction is of the programs between HEW, NIH, and the Health Services Administration with relation to sickle cell disease?

Dr. RINGLER. Yes, sir.

The lead agency for this program within HEW is our Institute.

Mr. STOKES. NIH?

Dr. RINGLER. NHLI, which is a part of NIH. One major segment of the program is in the Health Services Administration. That program is funded through the appropriation that this committee makes available to our Institute and the funds are transferred to the Health Services Administration to carry out what we call the sickle cell clinics program.

The purpose of those clinics is to develop and field test methodology for screening and counseling techniques. We have 26 such clinics. The rest of the program is primarily within NHLI in NIH, and a training program in hemoglobinopathy testing techniques run through CDC.

The total effort is referred to Dr. Rudy Jackson, the Sickle Cell Coordinator.

I can go into further detail if you would like.

Mr. STOKES. I would like to hear more.

Dr. RINGLER. The program within NHLI has several segments. One segment is the large comprehensive sickle cell centers. Those are concerned with research in the usual sense of the word. They are also concerned with the bringing through application, if you will, the results of research.

Hence, they have been very active in developing screening methodology, better methods for directing the sickle hemoglobin and related-hemoglobin variants. They have also been concerned with public education in the area of sickle cell disease.

So the centers would be a second component. We have what would normally be referred to as a targeted program in the area where an attempt is made to evaluate specific agents in their ability to reverse the vaso-occlusive sickle cell process. You may remember a few years ago a drug called urea was investigated for its ability to reverse the sickle cell process. That did not work. We now have sodium cyanate in the experimental stage.

Another aspect of the program is in the area of education. We do try to do this in coordination with the CDC. Again this involves the development of educational materials specifically for sickle cell trait and sickle cell disease. Another segment of the program is a training program for medical technologists where they can go to CDC or, if there is a large enough number of them, a representative from CDC will come to their community to teach the lab technology one needs to know in order to screen for sickle cell.

Mr. MILLER. Mr. Stokes, is it clear that there is no other effort in HEW than the one Dr. Ringler has described. The Heart Institute is responsible for coordinating the entire effort. That is the single program.

PROGRESS IN THE SICKLE CELL PROGRAM

Mr. STOKES. You are right. I think the record should reflect that fact. Is there any way that we can assess what type of progress is being made with reference to really bringing relief in the total picture?

Is it pretty difficult to make any real assessment?

Dr. RINGLER. I suppose one way to approach that would be for us to prepare a short statement for the record that would indicate the accomplishments since the program was initiated roughly 3 years ago. From my viewpoint I can highlight a point or two that will turn out to be examples. We had what we called the first National Conference on Sickle Cell Disease last spring. This was rather widely publicized.

We received responses from some 700 investigators who wished to report on research projects relating to sickle cell anemia. In my personal judgment had we had such a conference three years ago and asked for a solicitation of abstracts to be presented, I think the number of responses would have been very small indeed. So I think the interest in working on problems relating to sickle cell anemia has grown tremendously. To me that is one fairly big measure. I think the education story is being gotten out in a much better way. I will develop a fuller answer for the record if you would like to have use do so.

Mr. STOKES. I would be glad to have that for the record.

[The information follows:]

SICKLE CELL DISEASE—ASSESSMENT OF ACCOMPLISHMENTS

A number of achievements have occurred since the initiation of the Federal sickle cell disease program in 1971. Highlights of these accomplishments include:

(1) The development of more accurate means to identify the presence of sickle and other abnormal hemoglobins at birth, including a new procedure which will also identify the presence of the hemoglobin which leads to the occurrence of the thalassemia states. These developments will now permit the diagnosis of sickle cell anemia and other hemoglobinopathies in the immediate newborn period thus providing the physician and patients with information which will assist in the early care and treatment of these infants;

(2) The standardization of the diagnostic approach to sickle and other abnormal hemoglobins thus allowing for an approach which will yield the greatest amount of information and an approach which will be uniformly used by all laboratories. This approach essentially is the utilization of electrophoretic techniques as the primary approach followed by a confirmatory procedure in the case of sickle hemoglobin;

(3) The establishment of a hemoglobinpathy workshop program which provides training and instructions on the identification of abnormal hemoglobins for any interested laboratory technicians at the Federal, State, or local level. In addition, a proficiency testing program has been established to improve the quality of results reported from all laboratories supported through the Federal sickle cell disease program as well as any other lab interested in participating in the program;

(4) The support of controlled therapeutic trials utilizing urea and alkalis showing that neither is efficacious in the treatment of the painful crises which occur in persons with sickle cell anemia;

(5) The provision of grant and contract support to researchers and demonstration projects to study the underlying mechanism of the sickling process, the complications and sequelae of the disorder, antisickling agents, and means of improving the effectiveness of education, testing, and counseling processes;

(6) The catalyzing of the formation of the Hemolytic Disorder Study Group, an organization of researchers whose major purpose is that of addressing the problems of sickle cell anemia, thalassemia, and other disorders which alter the lifespan of red blood cells. This group provides advice to the program in numerous areas including therapeutic approaches for the sickle cell disorder;

(7) The sponsoring of the First National Symposium on Sickle Cell Disease by NIH in June, 1974, in which over 115 papers were presented allowing for an assessment of research in progress in sickle cell over the past 3 years;

(8) The opening of the First Permanent Exhibit on Sickle Cell at the Museum of Science and Industry in Chicago, Ill., in March, 1975;

(9) The education of employers, insurors, physicians, allied health professionals, and the general public through an ongoing sickle cell education program consisting of various communication media, continuing education, seminars, etc. and;

(10) The improvement of general care of patients with sickle cell anemia including the encouragement of a comprehensive approach to the sickle cell patient's problems. This includes early detection of sickle cell complications and the involvement of behavioral scientists in the overall care of patients.

SUPPORT OF SICKLE CELL CLINICS THROUGH HSA

Mr. STOKES. Can you tell me what moneys in both amount and percentage of the Sickle Cell Branch, National Heart and Lung Institute, budget are allocated for the HSA service portion of the national sickle cell program.

Dr. RINGLER. Yes, sir.

The sickle cell branch this year at the level of our appropriation, namely $324 million will probably be expending on the order of $19 million. I say on the order of $19 million because that allocation has only recently become available to us and we have not fixed on the last word on the allocation.

Of that amount approximately $3.5 million would be for the Sickle Cell Clinics which are funded with our funds, but operate through the Health Services Administration.

Mr. STOKES. Are you talking about roughly 20 percent?

Dr. RINGLER. It is 3½ of 19. It is over 18 percent, Mr. Miller informs me.

Mr. STOKES. Is this amount really sufficient in order to be able to run what we consider to be viable HSA service programs?

Wouldn't you need at least $5 million to be talking about viability in terms of program?

Dr. RINGLER. That becomes a matter of judgment again of where the funds can most adequately be use.

The idea of those clinics was to set up demonstration projects that would be of a fixed duration, the period of 3 years was suggested, where we could demonstrate the methodologies for sickle cell screening and counseling after which the activity would be made a part of a total health multiphasic screening methodology where you would not only check for sickle cell but also for high blood pressure and several other things. That is a partial answer to your question.

Mr. STOKES. Let's pursue that a little further. In terms of the service clinics, is there any present plan to phase them out at some particular stage or what exactly is the plan?

Dr. RINGLER. As I indicated previously, the plan within the program was to begin phasing them out after 3 years, which would be beginning next year.

The thought was that rather than support large numbers of categorical screening programs we should attempt to make them part of a total system as we discussed here a few moments ago. This has been the overall plan.

Mr. STOKES. Will that result in a large number of people not being able to receive treatment?

Dr. RINGLER. It should not. It should improve the situation. The clinics we have are not intended to be clinics set up to provide services in the usual sense of the word. They were set up to prove, if you will, the screening methodology so that it could then be used by health service systems in a broader screening context.

AUTHORIZATION FOR SICKLE CELL PROGRAM

Mr. STOKES. Let me ask you about Public Law 92–294, which in 1971 authorized $50 million in the Sickle Cell Anemia Control Act of 1971 under which there have never been any appropriations.

You had never sought any appropriations under that act either, have you?

Dr. RINGLER. I guess the answer to that is "No."

Let me just add to that by saying that we do have authority under the National Heart, Blood Vessel, and Lung Act for that type of activity. There are two authorizations for that type of activity.

Mr. STOKES. Right now as I understand it, all the money that you allot to sickle cell and I guess it is somewhere around $16 million at this point, both on research and services aspects, all of it comes solely out of the appropriation you get from this committee.

Dr. RINGLER. That is correct.

Mr. STOKES. But actually there is another source now under 92–224, had you pursued it? What I am trying to find out is, in light of the fact there would have to be no crediting of the funds received here under this other act, why have you not attempted to get additional funding for the program there?

Is there any explanation?

Mr. MILLER. It gets very technical, Mr. Stokes. Generally what we do in situations like this, and it occurs throughout our appropriations, is if there are several authorities under which we can obtain funds, we cite them in the appropriation language and all of the funds would be considered by this subcommittee and would go to this Institute. We try not to distinguish between laws because we want the flexibility to distribute the appropriations to meet research needs.

I think what you are driving at is the level of appropriations to the Heart Institute rather than the authorities under which we seek it. We have no problem using the money that you appropriate under the new law.

Mr. STOKES. The only thing I am getting at is, I suppose that gives you a higher level of funding in terms of this particular program.

Dr. LAMONT-HAVERS. Except that the authorization of section 301 is open ended, Mr. Stokes, so there is no authorization limit on what is thought necessary, as far as the appropriation is concerned.

Mr. MILLER. 301 is our general research authority at NIH.

Dr. LAMONT-HAVERS. So you could go as far as you like, as far as the appropriation is concerned, under that law.

HYPERTENSION PROGRAM

Mr. STOKES. I see.

Now under your hypertension program, and you can supply this now or supply it for the record if you like, I would like for you to go into some discussion for me in the record with reference as to how many Americans are affected by the disease; how many have hypertensive heart disease, the prevalence of high blood pressure among black males, the death rate of persons affected by the disease, the question of whether the death rate for blacks is higher and the reason for this disparity between the races.

I would like to have you tell us what we are doing about it both in terms of research and treatment and then I would like to have some elaboration, if you will, on what type of success we are having in terms of the total program.

Can you supply that for the record?

Dr. RINGLER. We will be glad to provide it.

[The information follows:]

ANSWERS TO QUESTIONS ON HYPERTENSION

Q. How many Americans are affected by the disease?

A. Approximately 23 million Americans (15 percent of the general adult population) are estimated to have some degree of high blood pressure. A higher proportion of the adult black population—25 percent—is afflicted with the disease.

Q. How many persons with hypertension have hypertensive heart disease?

A. According to the 1960–62 national health examination survey, about one-half of the 23 million with hypertension have hypertensive heart disease.

Q. What is the prevalence of high blood pressure among black males?

A. As indicated, approximately 25 percent of the adult black males have hypertension.

Q. What is the death rate of persons affected by the disease?

A. According to data published by the National Center for Health Statistics in 1973, hypertensive disease mortality rates are as follows:

MORTALITY RATES

Per 100,000

Age	Whites	Others
Men:		
25 to 44	0.6	6.2
45 to 64	7.3	37.4
65 and over	72.0	122.7
Women:		
25 to 44	.5	5.4
45 to 64	5.0	30.6
65 and over	67.7	113.4

Q. Is the death rate for blacks higher? Why?

A. As shown in the table above, the death rates for blacks are markedly higher than for whites. The reasons for this have not been clearly identified and verified. It is known that hypertension tends to appear at a younger age among blacks and tends to be more severe. We do not know whether this is due to genetic characteristics, or such environmental characteristics as diet, stress, socioeconomic factors, or other causes. A number of research studies are underway, including laboratory, clinical, and epidemiological research, seeking to identify possible causes for these differences, but it cannot yet be said that we have any definitive findings in this area. In addition to possible differences in the causes of the disease, it is clear that blacks in general have had less access to health care and preventive services; some of the excess death rate may be attributable to this fact alone.

RESEARCH AND TREATMENT

The last 10 or so years have seen a dramatic improvement in our ability to control high blood pressure. We have not yet found the causes of the disease, so we have not developed effective measures to prevent it from occurring. But once it does occur, we have a wide variety of drugs that can be taken to keep the pressure down for most people. These drugs and treatments are in standard medical practice. Research is continuing on the causes and prevention of hypertension, as well as on the development of even better drugs for its control. A major problem in hypertension presents itself, not in knowing how to treat it, but getting people to take the effort to determine whether they have it and if they do, to take the available measures to control it and prevent or reduce its toll. This, of course, is the major task and challenge faced by our national high blood pressure education program. Special efforts are being directed in that program at reaching blacks. In one of our major clinical trials, the hypertension detection and followup program, 26 percent of the persons screened for hypertension were black, and slightly more than 40 percent of the persons who are being treated in that program are black.

In HDFP, the percentage of blacks who were found to have hypertension (or were under treatment for it) at initial screening was twice as high as the percentage of whites: Black men, 36 percent; black women, 38 percent; white men, 19 percent; and white women, 18 percent.

Mr. STOKES. Let me ask you about this. I saw something I thought was rather interesting. In terms of your hypertension program, in an earlier report submitted to our committee you make this statement regarding the consumer education:

Consumer education efforts include creation of a mass media campaign featuring popular celebrities, Jimmy the Greek and Ann Landers, and distribution materials to TV, radio, mass circulation magazines, and newspapers resulting in a minimum of $4.1 million in free public service television time and $640,000 in free radio time for NHB–PEP messages to date.

Now, are there some other popular celebrities you use besides Jimmy the Greek and Ann Landers? Do you use anybody like Harry Belafonte or Pearl Bailey?

Dr. RINGLER. Unfortunately, I cannot list for you all the people we have sought to help us tell the hypertension story. I can have it expanded for the record. Specifically, I don't know if we have used the two people you have mentioned or not. I just don't know.

Mr. STOKES. Not that I have anything against either one of them, but I do not relate very well to Jimmy the Greek, and I don't think most black people do.

Dr. RINGLER. I understand the point you are making. I will check it when I get back, and I will submit something on the record about it.

We have tried to have the program responsive to the black community because there is a substantial amount of high blood pressure in the black community. If we have not been sensitive to that point, we should have been. Let me check on it.

Mr. STOKES. I would really appreciate it.

[The information follows:]

The national high blood pressure education program (NHBPEP) both within the National Heart and Lung Institute and also among participating organizations employs a number of celebrities in public education messages in addition to Jimmy the Greek Snyder and Ann Landers. Examples are (1) Michael Evans (Lionel on the Jeffersons TV show), (2) Jack Webb (Dragnet), (3) Pearl Bailey (through Citizens for the Treatment of High Blood Pressure in cooperation with NHBPEP), (4) Johnny Carson (through Citizens for the Treatment of High Blood Pressure in cooperation with NHBPEP), (5) Nipsy Russell (American Medical Association in cooperation with NHBPEP), (6) Bill Bixby (American Heart Association/NHBPEP), (7) Stiller and Meara (AHA/NHBPEP), (8) Ricardo Montalban (AHA/NHBPEP).

In addition the program has used other spokespersons relating specifically to hypertension (for example, Hazel Swann, M.D., chairperson, Commission on High Blood Pressure of the National Medical Association; Harriet P. Dustan, M.D., vice chairman of the Research Division of the Cleveland Clinic and clinical professor of medicine at Case Western Reserve University).

The program's consumer education messages are directed to general audiences, aware hypertensives, black and Spanish-speaking Americans.

Mr. MILLER. Mr. Stokes, could I go back to the previous question and say that the appropriation language we have proposed to this subcommittee does cite the public law you have referred to on sickle cell anemia.

Mr. STOKES. Fine. That is an area in which, in which I have a great interest. I have in fact testified before the subcommittee and asked them to consider an additional line item in order to see that we put additional funding into that area.

LEVEL OF FUNDING IN HYPERTENSION PROGRAM

Mr. STOKES. Can you give me some idea under your hypertension program as to what kind of money we put into research in 1974, into treatment and into education and also what your budget provides for 1975 and 1976.

Dr. RINGLER. Again, if I may, I would like to submit those for the record. It is an order of magnitude, the total program, something like $40 million in 1976, on the order of around $3 million will be for the high blood pressure education program.

There must be eight or nine in the demonstration control area and the rest would be in research. In the interest of having it be accurate, I would like to submit the numbers for the record.

Mr. STOKES. That would be fine, Doctor. Thank you very much.

[The information follows:]

BUDGET FOR HYPERTENSION

Obligations for NHLI hypertension programs totaled $47.4 million in 1974. Comparable figures for 1975 and 1976 are $39.5 million and $35.5 million. These figures differ somewhat from previous figures submitted in the special report on "High Blood Pressure (Hypertension)". This is the result of a recently completed review of 1974 data, which has resulted in a reevaluation of 1975 and 1976 estimates as well.

A summary of 1974 hypertension programs follows:

Hypertension activities:	*Millions*
Regular research grants	$21.0
Hypertension education grants	1.0
Training programs	2.4
Segment of multiple-risk factor intervention trial	5.1
Hypertension detection and follow-up program	11.1
Hypertension information contracts	.9
Hypertension etiology and other clinical applications	.8
Laboratory and clinical research	2.7
Research management and program services	2.4
Total	47.4

NHLI CUMULATIVE OBLIGATIONS

Mr. CONTE. Doctor, you have spent over $1,500 million so far on heart and lung disease.

Dr. RINGLER. It was established in 1948. I suspect it is a little over $2 billion since then.

Mr. CONTE. Then you have also had quite a bit of money coming in in the same area from the outside private donors?

Dr. RINGLER. It does not come to the Institute but you are referring to the American Heart Association, for example.

Mr. CONTE. Right.

How much would you estimate?

Dr. RINGLER. I would estimate on the order of $38 to $40 million.

Mr. CONTE. Per year?

Dr. RINGLER. Yes.

Mr. CONTE. This thing bothers me as I sit here and listen, and somebody says your budget is a little less than last year. What if I gave you $5 billion this year, would you be able to come up with a cure in the next 12 months?

Dr. RINGLER. No, sir.

Mr. CONTE. Of course not.

We have to establish our priorities here.

Do you feel you have enough money here to carry out your research? If not, where are you impaired?

ADEQUACY OF FUNDING

Dr. RINGLER. Let me answer that as follows:

I suspect any institute director who comes before you can identify things that he would like to do. Most of us even in our private lives can identify things we would like to have.

Mr. CONTE. Of course there is no end to it. People have an insatiable thirst.

Dr. RINGLER. I can identify a great many things I would like to see done. I also recognize that somebody above me must put them in some sort of perspective and must oversee the total Federal allocation of expenditures. My personal view is as long as I can have a hearing with the people on my right about what my share of the total package should be, I think that is a reasonable way to deal with it.

RECENT ADVANCES

Mr. CONTE. What did you accomplish the last 12 months with what we gave you?

What breakthroughs did you make?

Dr. RINGLER. The word "breakthrough" is a difficult word.

LESSENING OF DAMAGE TO HEART MUSCLE FOLLOWING HEART ATTACK

Mr. CONTE. How about some advances, then?

Dr. RINGLER. There have been some substantial advances in the last 12 months, but it is easier to talk about them in the terms of a year or two because research works over the years.

One example is the amount of damage that results to the heart after a heart attack. It used to be felt after a heart attack X amount of the heart muscle is dead and gone. Now the medical community has determined that that is not true, that the amount of damage following a heart attack is not fixed at the time of the attack but that the area of infarction enlarges over the next period of several hours and even up to as much as 24 hours. Once having made that observation, it is possible to develop techniques that minimize the extent of damage and the amount of disability resulting from the heart attack.

I think there would be a wide consensus of opinion that the potential for minimizing and lessening the amount of damage to heart muscle is very substantial, indeed. We have about 1.2 million heart attacks in this country each year. If you look forward to lessening the amount of damage to 1.2 million hearts per year I think that is a pretty big accomplishment.

Mr. CONTE. Who came up with this discovery?

Dr. RINGLER. The advance is shared by several people. I suspect that the original credit should probably go to the cardiology group at the University of California at San Diego. The head of the group at that time was Dr. Gene Braumwald.

Mr. CONTE. How much of a grant did we give him?

Dr. RINGLER. I think it was on the order of perhaps $800,000.

Mr. CONTE. That is peanuts compared to your total budget.

Dr. RINGLER. He was doing many things in addition to the one project I just made reference to.

Mr. CONTE. It was still a very, very small amount of the entire budget that you are asking for.

Dr. RINGLER. That is true.

UNDERSTANDING BASIC FUNCTIONS OF THE LUNG

Mr. CONTE. What other advances or discoveries—whatever you want to call them if you don't like the word "breakthrough," use your own noun—can you point to?

Dr. RINGLER. There have been very important breakthroughs in lung disease, better diagnosis, better understanding of the causes of lung disease. By and large over the years we have had good documentation of the effect of the disease but we have not been able to understand very much about the cause of the disease, with the exception of acute infections, colds, pneumonia, et cetera, we have not understood the effect of the disease. I think one of the major contributions from the money invested in the lung area has been improved understanding of the basic functions of the lung.

That is another example.

ADVANCES IN BLOOD RESEARCH

If one goes to the blood area, then several things come to mind. One is in the area of the hemophiliac. In recent years and within the last year or so, the preparation and storage of so-called antihemophilic factors that hemophiliacs require to control their bleeding episodes have improved substantially.

We now talk in terms of home care where a hemophilic can take a unit of this antihemophilic factor and keep it at home and even take it with him on vacation. I think that is a very substantial breakthrough.

REDUCTION OF IN-HOSPITAL DEATHS FROM HEART ATTACK

A different kind of breakthrough I would like to refer to over a somewhat longer duration, say, take a period of about 10 years; 10 years ago hospital mortality following a heart attack was about 30 percent. Today, 1975, it is about 20 percent. That is a one-third reduction in in-hospital deaths from heart attacks. When one does the arithmetic to see how many people are now living to leave the hospital whereas 10 years ago they would have died, recognizing the huge number of heart attacks we have in this country, the numbers are very substantial. I think that is another breakthrough.

REDUCTION IN HOSPITAL STAY FOLLOWING HEART ATTACK

The third type is the amount of time you stay in the hospital following the heart attack. It used to be routine that you stayed 3 weeks or more. Today the average stay is 16 to 17 days for a heart attack. If one does the arithmetic of something like 500,000 people a year being discharged from a hospital, at $150 a day for a period of hospitalization, that comes to a savings to somebody in terms of decreased cost of hospital care that comes out in the hundreds of millions of dollars.

RESEARCH SUPPORT

Mr. CONTE. A lot of those breakthroughs come about through private institutions doing their own exploratory work, doing their own research. It could come out of some small hospital, some doctor who gets no grant at all.

Dr. RINGLER. That is true. I would feel that the vast majority of them in this country do come from investigators supported by our Institute because our system is such that the major source of support for research in this area is our Institute.

In the private sector it is the American Heart Association.

FOREIGN SUPPORT IN HEART AND LUNG DISEASES

Mr. CONTE. What other country spends quite a deal of their resources in the study of heart and lung disease?

Dr. RINGLER. I cannot give you dollar levels in relationship to their GNP or somthing like that because I do not know their fiscal situation. Countries like Sweden, for example, Great Britain, Germany in particular, Japan, all of them have very substantial research programs in this area. I suspect that percentagewise the dollars invested or currency invested is much less than it is in this country. I know that as a matter of fact.

MAGNITUDE OF RESEARCH SUPPORT

Mr. CONTE. I am a great advocate of this research. I support these expenditures but it troubles me when you say $2 billion since 1966.

Dr. RINGLER. I'm informed that since 1966 we have spent $1.7 billion.

Mr. CONTE. All right, that is just about what I said. That is a lot of money. You are only one Institute. Then you have all the other institutes.

Dr. RINGLER. I might point out that our Institute does cover heart diseases, lung diseases, blood diseases, and it does cover blood banking. So it has a big piece of the total research pie.

COOLEY'S ANEMIA

Mr. CONTE. Last year we were told you were working on the development of effective screening tests for Cooley's anemia. What is the status of that?

Dr. RINGLER. We are currently attempting to develop a better screening test for Cooley's anemia. That is a very difficult task if you want to develop a test that meets the usual criteria for screening tests, that is something simple, inexpensive and something that can be applied in a situation where there are no highly trained, highly skilled screening personnel. We still have a ways to go before we realize such a screening method.

Mr. CONTE. Have you made any progress with regard to Cooley's anemia?

Dr. RINGLER. The answer to that is yes on two counts: One, we have underway within the Institute now a pilot clinical trial to test an agent, an iron-chelating agent to get rid of the overloading problem that results from the frequent transfusions these patients receive. Our plan is to expand that into a comprehensive clinical trial of this agent

within the next few months. Two, within the Institute's intramural program there is a very good effort to understand the elements of hemoglobin synthesis. We do have now, within Dr. French Anderson's laboratory, the understanding of each of the steps in hemoglobin synthesis. This gives us the potential of trying to influence that process by hopefully at least being able to minimize the defect which causes this, inadequate hemoglobin synthesis which causes the problem in the first place.

We are a long ways from being there, but I think progress is being made.

ARTIFICIAL HEART DEVICES

Mr. CONTE. Did you talk about the artificial heart program and what stage of the research you are in in the artificial heart program before I came in?

When can we look to some proven results?

Dr. RINGLER. No, we did not talk about it before you came in, Mr. Conte. Where we stand on that now is, we have a left-heart assist device, a device that will replace the left part of the heart, the part that pumps the blood to the systemic circulation. It may be reaching a point of first clinical application.

The reason we have shifted the emphasis to a left-heart device as opposed to a total heart is because the data would indicate that the overwhelming majority of pople who could profit by a total heart could profit equally well by a left heart. Complications of developing a left-heart assist device are far less than replacing the total heart.

In other words, I am saying that in 80-or-so percent of the cases the part of the heart that fails is the left side of the heart and the mechanical device would be a replacement for that one chamber of the heart.

The devices we have in mind have undergone extensive animal testing. At the moment they are undergoing a final series of animal tests.

Based on that data a decision will be made as to whether it is appropriate to go forward with very limited clinical applications under well defined circumstances.

Mr. CONTE. We have not gone beyond the animal stage?

Dr. RINGLER. No, not yet.

Mr. CONTE. Thank you, Doctor.

HYPERTENSION INCIDENCE AND PROGRAMS

Mr. CONTE. What percentage of the population do you estimate suffers from hypertension? What portion of those people are being reached by the national high blood pressure education program?

Dr. RINGLER. Approximately 15 percent of the general adult population, according to information from the national health examination survey, suffer from hypertension. Approximately one-fourth of the adult black population is afflicted with this disease.

It is difficult to assess precisely the numbers of those persons being reached by program efforts inasmuch as the effort is multifaceted. There is clear evidence that more people are seeing their physicians for hypertension and that the use of hypertensive medication is increasing. In terms of awareness, we estimate that approximately 200

million potential viewers have been exposed to messages developed by the National Heart and Lung Institute alone. Please note that we are using the term "viewer exposures" and not individual persons. If one includes also additional participants in the program such as the American Heart Association, American Medical Association, American Osteopathic Association, Citizens for Treatment of High Blood Pressure, Inc., Blue Cross/Blue Shield, and others who have produced public service materials, it is reasonable to assume that this figure is between 5 and 8 times higher for the cumulative effort of the program. Estimates for radio listeners time are approximately of the same magnitude. Print media is more difficult to assess inasmuch as we lack resources for exhaustive information gathering. However, we can report that during High Blood Pressure Month, May 1974, over 15,000 newspaper clippings were collected, which related to high blood pressure control and High Blood Pressure Month.

The national high blood pressure education program is also attempting to reach the health professional segment of the population. Since the inception of the program the number of journal articles relating to hypertension has increased approximately fivefold. In addition, a number of journals, including the Journal of Urban Health, Journal of the American Pharmaceutical Association, Patient Care, and a variety of others have carried special issues in which hypertension was the total focus of the issue. Guidelines for hypertension therapy are being circulated to the entire membership of the American Academy of Family Physicians, a group with a membership of approximately 35,000 physicians. Recently, the American Dental Association passed a resolution endorsing the concepts of the national high blood pressure education program and supporting continuing education on hypertension control for all dentists. Through this mechanism the entire dental profession is being reached. Both the National League for Nursing and the American Nursing Association Journals have carried a number of articles on hypertension, and these organizations are currently participating jointly with the National Heart and Lung Institute in a task force to specifically define appropriate roles for nursing in hypertension control.

Mr. CONTE. Have their been any advances in the control of high blood pressure during the year? Would you describe them?

Dr. RINGLER. During 1972, data available to us indicates a 15-percent increase in the number of patient visits for hypertension and hypertensive heart disease. During 1973, there was an additional 20-percent increase in these visits. During 1974 we experienced only a 3-percent increase. The relative number, of new visits and prescriptions written for hypertensive medication follow an approximate parallel rate of increase. These data suggest that those who are readily receptive to the message of the program have responded, and that we now face the task of motivating the hard core of skeptical and apathetic persons in the population. We believe that the number and effectiveness of community programs has increased since the inception of the program in 1972. However, once again a lack of resources for the substantial data gathering effort required to make this assessment does not permit us to report this activity in terms of specific validated numbers. It can be said, however, that during the first High Blood Pressure Month in May 1974, and for the current High Blood Pressure Month,

May 1975, over 100 national organizations have committed participation in writing as have over 300 community organizations.

No new scientific breakthroughs have been made during the year in terms of new drugs available or new methods of therapy.

NATIONAL RESEARCH AND DEMONSTRATION CENTERS

Mr. CONTE. You mentioned your three national research and demonstration centers. Where are these centers located? Could you go into more detail about the activities of these centers?

Dr. RINGLER. The NHLI has activated three national research and demonstration centers—a Research and Demonstration Center for Heart and Vascular Disease at Baylor College of Medicine, the Vermont Lung Center at the University of Vermont, and a Community Blood Resource Center at the King County Central Blood Bank, Seattle, Wash.

The research efforts being pursued at Baylor are laregly devoted to arteriosclerotic disease and comprise three distinct but interrelated areas. They are basic and clinical research, education, and demonstation activities. The projects in the education and demonstration areas cover a broad scope of endeavors aimed at reducing the morbidity and mortality of cardiovascular disease. I would like to enumerate projects which exemplify this. In secondary and university education self instructional materials on cardiovascular disease including risk factors and preventive measures will be developed for students and their parents. A program of continuing education for physicians and other health care practitioners will be developed. An assessment of existing attitudes, levels of knowledge and values of the public with respect to cardiovascular disease and their media habits is being carried out through a survey which will provide baseline data for the development of all the other center projects. The accessibility and cost of health services of cardiovascular patients in neighborhood clinics will be determined through several protocols designed to shift the emphasis from episode to preventive care. A cardiac work evaluation unit and reconditioning exercise program will be established in a neighborhood clinic and evaluated. A telemetered ambulance system will be evaluated to determine whether it increases the number of heart attack survivors. A public education component will educate people regarding the signs and symptoms of a heart attack and emergency measures which can be instituted. A variety of persuasive communications will be developed for films and role-playing sessions to be used in elementary and secondary schools to reduce or deter smoking in schoolchildren. A program of dietary education for community groups is being established to lower plasma cholesterol and triglyceride concentrations as a means of reducing their risk of coronary heart disease. Efforts are underway to standardize the clinical laboratory assay procedures for total cholosterol and triglycerides in participating laboratories in an attempt to improve the care of patients.

The Vermont Center will coordinate the activities of several groups, including the State department of health, the Vermont Lung Association and members of the Department of Community Medicine, Continuing Medical Education, Medicine, Pathology and Physiology of the University of Vermont School of Medicine. The center will act as a prototype system for training, education, treatment, and prevention in

the field of respiratory disease. Specific activity and targets include an interdisciplinary study of the prevention and control of pneumoconiosis, research in the pathology and management of acute plumonary trauma, in basic methodology of computer-assisted instruction in pulmonary physiology, in the pathology, pathogenesis, biochemistry, immunology, and cell physiology of diffuse interstitial lung disease, clinical demonstrations and applications of research findings of lung disease using the problem-oriented medical information system, demonstration of regional management of specified lung disease problems in utilizing an interhospital computer network, demonstration of graduate and postgraduate educational methodology using audiovisual aids and regional interactive television, dissemination of information to the public relating to lung disease problems specified by the regional Lung Disease Management Committee, and provision of a broadly based multidiscplinary training environment for the undergraduate, graduate and postgraduate scientists and health professionals in research, clinical practice, teaching and continuing education related to the etiology prevention, diagnosis and treatment of diseases of the lung.

The National Research and Demonstration Center in Seattle deals with blood and blood resources. As the name "research and demonstration" indicates, this program stands as an interface between univercity-oriented scientific research and community-oriented education and service activities. The Center demonstrates a variety of efficient systems for obtaining, preserving, and delivering safe blood and blood products to a sizable geographic segment of the Pacific Northwest and is a national model in this regard. In addition it is developing and implementing educational techniques which reach such diverse audiences as school children, technicians, and practicing physicians. The research efforts, primarily in coagulation, blood preservation and management techniques are already recognized nationally, but what is unique about this program is the mechanism to put research discoveries into practice rapidly and effectively.

EARLY WARNING FOR HEART ATTACK RISK PATIENTS

Mr. CONTE. I have seen some articles about efforts to establish criteria for early warning identification of heart attack risk patients. What sort of work is being done in this area?

Dr. RINGLER. Identification of high risk persons can be described in two phases. First is the identification of persons who have any of the risk factors that have been identified by research in the past, particularly through the research conducted at the Institute's Framingham project for the past 20 years. The major risk favctors are high blood pressure, elevated levels of lipids in the blood, and cigarette smoking. Not everyone who has one or more of these characteristics suffers a heart attack, and conversely, some people who have heart attacks do not have any of these characteristics. Nevertheless, these are fairly good predictors of a significant proportion of heart attacks.

The second phase of identification relates to more precise indications of an imminent or beginning heart attack. The early warning symptoms of a heart attack can be very catastrophic and unmistakable, such as collapse of the individual, or very nonspecific such as what is

interpreted by the person as a minor "heart burn" or indigestion. Some research investigators are focusing on the period from 3 days to 3 weeks immediately prior to a heart attack, searching for clues as to changes in the person's habits or life style which would serve to alert either the patient or his family to the possibility of an impending heart attack. Thus far, the changes noted have occurred with some frequency but are nonspecific in their character. For example, many of these patients complained of extreme fatigue in the days prior to the acute event. Since many patients who die from a heart attack do so suddenly, apparently from an irregularily in the heart's electrical rhythm, much work is being directed at those individuals who seem to be particularly prone to developing this irregular rhythm. Such studies include investigating the value of monitoring a patient with devices which are sensitive to irregularities in rhythm and which by some electronic signal, such as a beep, warns the patient that he is having some irregularity of heart beat. He then might contact his physician for verification and for further instruction.

TREATMENT FOR CORONARY HEART DISEASE

Mr. CONTE. In your discussion of coronary heart disease treatment through coronary bypass, you said that this was the radical approach. Would you tell me what the less radical treatments entail?

Dr. RINGLER. These less radical means of treatment include behavior modification, such as cessation of smoking and avoidance of stress; the administration of drugs which dilate the coronary arteries or reduce the heart's workload; treatment of hypertension with drugs; the use of diuretics, drugs that help the body excrete excesses of salt and fluid, which are involved in congestive heart failure; the use of digitalis which works to strengthen the heart muscle's ability to contract; and dietary manipulation to reduce elevated blood cholesterol and obesity.

DISSEMINATION OF INFORMATION—CORONARY DRUG STUDY

Mr. CONTE. In conjunction with your new health information programs, you spoke of a direct communication to physicians on the history of heart attack. When is this going out? Is this the ordinary procedure for disseminating information?

Dr. RINGLER. There have been a number of communications directed at physicians and the general public about the conduct and results of the coronary drug project. When the study was started, some 10 years ago, much of the original patient recruitment was done through direct communication to physicians in the area of the 53 research clinics in the study. When the major findings were announced early this year, the definitive scientific summary of the project was published in the Journal of the American Medical Association, the basic and widely circulated medical journal. The NHLI organized a press briefing held in January 1975 announcing the findings of the study. As a result of this briefing, reports of the study appeared in A.M.A. News, Medical World News, U.S. Medicine, Medical Tribune, Science, and Lancet. These publications have a total circulation of nearly 1 million. A further report is being prepared by the Medical Letter, a nonprofit medical-pharmacology briefing.

A taped interview was aired by the Physicians Radio Network. Dr. Robert I. Levy, director, Division of Heart and Vascular Diseases, and Dr. Jeremiah Stamler, chairman, Coronary Drug Project Steering Committee, summarized the results of the study. The New York Times, Chicago Tribune, and United Press International also featured CDP results. At an open public meeting of the National Heart and Lung Advisory Council the entire project and its results were presented.

The Institute has determined that the most appropriate means of informing physicians of the results of the study in relation to the specific drugs covered in the study would be through the Food and Drug Administration. We are working with FDA on informational material to be sent out by FDA in its Drug Bulletin and in the appropriate drug insert.

This wide array of methods and avenues of communicating results of NHLI research represent several of the methods used for disseminating information. On occasion, other additional methods are used, such as publication and distribution of Institute publications. These methods are, of course, supplemental to the standard scientific practice whereby scientists publish results of their research in a wide variety of scientific, medical, and technical journals.

COMPARISON OF INCIDENCE OF HEART ATTACK

Mr. CONTE. Dr. Ringler, most other countries have a lower incidence of heart disease than the United States. What sort of investigations are being carried out in terms of relating differences between the United States and other countries to determining the causes of heart disease?

Dr. RINGLER. The Institute has long recognized the reported lower mortality from coronary heart disease in several countries and has supported specific cooperative studies to verify and seek explanation for such differences.

For example, beginning in 1956 the Institute provided support for a series of surveys to verify the reported differences in coronary heart disease in seven countries by an international cooperative study team led by Dr. Ancel Keys. Studies were organized and conducted in Finland, Japan, Italy, Greece, Yugoslavia, the Netherlands, and the United States. These studies examined more than 12,000 men aged 40 to 59 with standardized methods, used a central laboratory and central diagnostic evaluation to obtain comparability. The results of 5 years of followup of these 7 study populations revealed high coronary heart disease mortality rates for Finland, the United States, and the Netherlands. Low rates were found for the study populations in Greece, Yugoslavia, Japan, and Italy. The important factors that were significantly related to the low incidence were lower blood pressure levels, lower serum cholesterol levels, and some relationship to less body fatness. A 10-year follow-up experience is now in preparation. Additional cooperative studies between the staff of the Institute and researchers in Israel, Yugoslavia, Japan, and the United States based on standardized procedures conducted on more than 30,000 men followed for 7 years provide additional direct findings which confirm an incidence of coronary heart disease in Japan and Yugoslavia of only one-fourth that found in the Framingham study. Detailed information on many

factors as diet, physical activity, cultural patterns, and living patterns have been studied in addition to the established major risk factors. Results to date confirm the importance of levels of blood lipids, blood pressure, body fatness, diabetes, and socioeconomic level as important factors influencing the rate of development of coronary disease. Additional findings confirm urban-rural differences and these are being investigated further. However, even at equivalent levels of the major risk factors there is still a protective factor that needs explanation in understanding the low coronary disease rates in these populations.

LEADING CAUSES OF HEART DISEASE

Mr. CONTE. Are we pretty sure we know all of the causes of heart disease, or are there still possibilities under investigation? Would you just list the leading causes of heart disease, along with some indication of the proportion accounted for by that cause?

Dr. RINGLER. A great number of diseases, agents, and factors can cause forms of heart disease. While many of these have been identified, there will undoubtedly be more that will be discovered. Moreover, the causes of the major forms of heart disease such as coronary heart disease and hypertensive heart disease still remain to be fully understood. Many approaches to seek a basic understanding of the causes of these major diseases are under investigation and new hypotheses are emerging.

I would like to list the leading causes of heart disease as measured by their contribution to total mortality for the record.

[The information follows:]

PERCENT DISTRIBUTION OF DEATHS, HEART DISEASE, UNITED STATES 1973

Heart disease (ICDA code)	Number of deaths	Percent distribution
Total[1]	764,503	100.0
1. Coronary heart disease (410-413)	684,066	89.5
2. Hypertension and hypertensive heart disease (400-404)[1]	20,211	2.6
3. Active rheumatic fever and R.H.D. (390-398)	13,739	1.8
4. Other heart disease (420-429)	46,487	6.1
Acute pericarditis—nonrheumatic (420)	57	0
Acute and subacute endocarditis (421)	622	.1
Acute myocarditis (422)	413	.1
Chronic disease of pericardium (423)	503	.1
Chronic disease of endocardium (424)	1,107	.1
Cardiomyopathy (425)	2,378	.3
Pulmonary heart disease (426)	1,322	.2
Symptomatic heart disease (427)	27,057	3.5
Other myocardial insufficiency (428)	4,030	.5
Ill-defined heart disease (429)	8,998	1.2

[1] Includes 7,428 deaths due to hypertension (without heart disease), ICDA 400, 401, 403.

Source: National Center for Health Statistics.

ALLOCATION FOR LUNG PROGRAMS

Mr. CONTE. How much of your budget is being allocated for lung research programs?

Dr. RINGLER. Fifteen percent of the NHLI budget is being obligated for programs in lung research and training programs. This

amounted to $48.6 million in fiscal year 1974, an estimated $49 million in 1975, and a budget figure of over $44 million in 1976. These figures include extramural support in research grants and contracts, training programs, intramural research programs at Bethesda, as well as pertinent management and service costs.

SMOKING

Mr. CONTE. How much of lung research supported by the National Heart and Lung Institute is related to the dangers of smoking?

Dr. RINGLER. The problem of smoking is an important area of concern to the NHLI and at a conference to be held in May, to discuss the relevance of health behavior to cardiovascular, lung, and blood diseases, the Institute has selected smoking behavior as its major emphasis.

Studies of smoking are part of investigations of emphysema and bronchitis or fibrotic and immunologic diseases in 11 of the 17 Specialized Centers of Research grants supported in the lung area. In addition, 15 contracts and 5 grants for population, case control, or family studies of pulmonary diseases include examination of smokers compared with nonsmokers. Specifically addressed to smoking are four contracts to study the effects of smoking on chronic airways obstruction, one of the earliest changes in emphysema; two contracts have supported development of animal models which can be used for physiologic studies to learn the changes in the lung that result from smoking; and modification of smoking behavior is being investigated under a reimbursable agreement. Also, the NHLI has, in cooperation with the National Cancer Institute, supported work on developing a safe cigarette.

The investigator-initiated research program also includes research on the effects of smoking on lung injury, but these are part of other investigations.

The Institute also supports programs on the effect of smoking on heart and vascular diseases. As in lung research, portions of a number of research grants concern the relation of smoking and smoking products to coronary heart disease. Studies on the relationships of smoking to coronary heart disease, stroke, and obstructive pulmonary disease are included in each of the Institute's major epidemiological projects, which are seeking to determine the relative importance of a variety of risk factors in these diseases. The study of cigarette smoking in the development of arteriosclerosis and its clinical complications is an important part of the multiple risk factor intervention trial and is also being studied in the hypertension detection and followup study.

Mr. CONTE. What portion of lung diseases could be cured if people did not smoke?

Dr. RINGLER. It is generally accepted by those engaged in pulmonary research that smoking is a major contributing factor to many lung diseases. Fibrotic and immunologic lung diseases are exacerbated by smoking. Chronic bronchitis, a most prevalent pulmonary disease and the one with high morbidity in national terms, is generally believed to be a preventable on the absence of smoking. Overall, smoking is a major health hazard relative to most forms of pulmonary disease.

AMERICAN BLOOD COMMISSION—NATIONAL BLOOD DONOR SYSTEM

Mr. CONTE. Recently the American Blood Commission held its chartering convention. How will you be working with this group to develop a national blood donor system?

Dr. RINGLER. One of the most critical, immediate needs in establishing a first class national blood supply system is the implementation of an all-volunteer blood donation system. In an effort to meet this need, the National Heart and Lung Institute submitted a request for proposals on December 22, 1972, soliciting research proposals to study blood donor recruitment in blood service systems. This occurred during the evaluation of the American Blood Commission. Those proposals were not funded because we felt that the most prudent course of action was to await the outcome of current deliberations with respect to the formation of the American Blood Commission and its task forces. The American Blood Commission has been formed and has accepted the responsibility of implementing the national blood policy which seeks to establish an all-volunteer blood donation system.

We will be working with the American Blood Commission to develop a national blood donor system by first discussing with the ABC and its task forces approaches to establish an all-volunteer donation system. If studies on donor recruitment are needed, the request for proposals originally submitted will be resubmitted. The information needs in this area will be met by the blood establishment inspection and registration system, an information system which is being jointly supported by the Bureau of Biologics, FDA, and the National Heart and Lung Institute. The motivation of donors can also be attributed to a lack of training on those who recruit donors. We are, through this information system, making a special attempt to get information on the training needs in our national blood system.

At its Health Behavior Conference on May 12–15, 1975, one of the major problem areas which the Heart and Lung Institute will address will be the motivation of volunteer blood donors and motivation of nondonors. It is at conferences such as this where we get a greater appreciation for the donor motivation problem. This is a few of the ways we hope to work with the American Blood Commission in establishing an all-volunteer blood donation system.

COLLECTION AND STORAGE OF BLOOD AND BLOOD FRACTIONS

Mr. CONTE. What sort of research is underway in the collection and storage of blood and blood fractions?

Dr. RINGLER. Whole blood has been collected and used successfully for periods of 21, 28, or 42 days after storage in the liquid state depending on what kind of solution it is stored in. Red cells, however, can be stored for several years and used successfully. But once they are thawed they have to be used within 24 hours. We are supporting research for the development and testing of connecting devices which insure the sterility of frozen-thawed blood. This will make it possible to extend the outdating period of frozen-thawed red cells past the present 24 hours.

The collection and storage of other blood fractions are handled differently. Take the platelets, for example. We have contract-supported

programs to improve platelet transfusion therapy in two major areas. One, there is a search for the optimum storage conditions of platelets. If platelets can be kept at least 72 hours, storage can be maintained over a weekend interval. In addition, work has been done to attempt storage of platelets by freezing. This will allow storage for an indefinite period of time. The difficulty encountered in selecting a desirable chemical to use as a freeze protector should be resolved in the foreseeable future.

The white blood cells are even more difficult to store and use successfully. Harvested granulocytes are currently being obtained and transfused with apparent clinical benefit by methods such as cell separators and continuous flow filtration-leukophoresis. Clinical utility, however, has been severely limited by present inability to preserve and store granulocyte preparations for use at a later time. We are supporting five studies to develop a successful procedure for the preservation of granulocytes for transfusion.

The clinical use of blood components instead of whole blood provides means for utilizing the national blood resource with maximum efficiency and economy. The collection of blood components, however, presents some special problems. We are supporting research studies for the isolation and evaluation of new products from blood plasma fractionation and for the development of new methods of blood plasma fractionation.

BLOOD CONTAMINATION—VOLUNTARY BLOOD DONOR SYSTEM

Mr. CONTE. The problem of blood contamination is serious in many parts of the country. Would a totally voluntary blood donor system eliminate that problem?

Dr. RINGLER. Indeed, there is good evidence that blood from paid donors carries up to 10 times the risk of volunteer-donor blood. If the paid population is in a skid-row population or one with large numbers of drug addicts, the risk may be higher. While the risk varies in different areas of the country, there is little question that elimination of the paid donor will markedly improve the safety of blood and blood products. In fact, use of volunteer blood may well be the single most important step which can now be taken to decrease the risk of hepatitis virus contamination of blood products for transfusion.

HIGH PRIORITY PROGRAMS IN 1976

Mr. CONTE. What do you consider your Institute's three or four top priorities for the next year?

Dr. RINGLER. The Institute has undertaken three major clinical trials concerning arteriosclerosis and hypertension. These are the lipid research clinics program, the hypertension detection and followup program, and the multiple risk factor intervention trial. A primary priority of the Institute is to accomplish total patient enrollment and to proceed with full implementation of these trials. Just getting underway is another large-scale clinical study to determine if the regular ingestion of aspirin reduces the incidence of recurrent heart attacks in men and women who have already had a heart attack, the aspirin-myocardial infarction study. This study will also need to be fully implemented in the coming year.

The past year has seen the further development of work on factors that may be involved in hypertension. Much of this work has been conducted within the Specalized Centers of Research for Hypertension which are devoted to multidisciplinary research in high blood pressure. Applications for the continuation and expansion of these Centers have been solicited and their award will be made in fiscal year 1976. This continuation of the Hypertension Centers reflected the contribution the current Centers are making in a coordinated and focused research program, and indicates the favorable assessment by the Institute and its scientific advisers of the value of this program.

A variety of important programs are involved in improved understanding of the structure and function of the lung. We need to continue and expand base programs during the next year. An important priority in the Institute's lung diseases program is to expand research in basic scientific disciplines, such as molecular biology, biochemistry, immunology, and ultrastructural anatomy. Results of such research can lead to advances in combating all forms of pulmonary disease.

In blood diseases and blood resources, as you have indicated, an important goal during the next year will be the implementation of the national blood policy which seeks, among other things, the establishment of an all-volunteer blood donation system. We are working with the American Blood Commission on this. We will continue high-priority research into blood diseases and blood, and into the use of blood for clinical purposes, and into all aspects of the management of its resources in this country.

Of high importance is the continued development of our recent initiatives in prevention, control, and education programs in heart, blood vessel, lung, and blood diseases and resources. Many studies indicate that more aggressive application of existing knowledge will materially reduce death and disability from the complications of these diseases.

TRAINING PROGRAMS

Mr. CONTE. You are passing out the training grant program in favor of the National Research Service Award program. Could you tell us how these programs differ, and why the training grant program is being phased out?

Dr. RINGLER. Subsequent to passage of the National Research Service Award Act of 1974, these awards became the exclusive mechanism of support for research training. Existing graduate training grants and fellowships are being phased out and replaced by the National Research Service Awards. These awards, like their predecessors, will support institutional, as well as individual research training. They differ in that there are service obligations and pay-back provisions which are not a part of the prior award programs. In addition another important difference is that starting July 1, 1975, awards may be made only in subject areas where a documented need exists.

NHLI RESEARCH DISCIPLINES

Mr. CONTE. What are the academic disciplines from which you draw your researchers?

Dr. RINGLER. The major clinical and nonclinical disciplines represented are cardiology, surgery, hematology, radiology, pharmacology, pediatrics, physiology, biochemistry, biophysics, pathology, clinical medicine, genetics, nutrition, epidemiology and biometrics, bioengineering, molecular biology, and the social and behavioral sciences.

Mr. CONTE. What do you foresee the manpower situation being for the next several years in those disciplines?

Dr. RINGLER. The manpower needs and forecasts for medical research as a whole are currently under study by the National Academy of Science, and authoritative information will be forthcoming from these studies soon. However, the Institute has already had the benefit of a number of recent studies made by experts in various disciplinary fields specifically related to cardiovascular, lung, and blood research. These studies indicate that there is a net deficit of over 600 new highly trained cardiovascular investigators per year and approximately 200 each for lung and blood. Of particular concern to the Institute are the shortages in a number of disciplines most directly related to the new and expanded areas of research mandated by the Heart, Blood Vessel, Lung, and Blood Act of 1972. These shortage areas are epidemiology, biostatistics, behavioral sciences, population genetics, and nutrition.

NONCOMPETING/COMPETING PERIODS

Mr. CONTE. Your justification refers to a decrease of $32.5 million in noncompeting continuations because of completion or conversion to competing status. Why would a grant be changed from noncompeting to competing? How do you allocate grants between these two categories—what criteria do you use?

Dr. RINGLER. Modern research is a complex undertaking that requires complicated equipment, sophisticated techniques, and scrupulous attention to detail. Repetition of experiments is an essential part of the research process so that one can be certain that the methods are reproducible and accurate and so that one can be certain of both statistical and biological significance. To accomplish this, it is essential that adequate time be available for the research endeavor and that adequately trained scientific and technical manpower will be at hand.

These various factors are taken into account in the initial scientific and technical merit review of research project support that is currently recommended by our panels of consultant reviewers is over 3 years and may be as much as 5 years.

Under our single year appropriation, most of our projects are traditionally funded for 1 year only for 1 year's appropriated funds. The additional years of support recommended at the time of initial review are awarded year by year. These are what we term "noncompeting continuations." While critical scientific reappraisal is a continuing feature of all programs, these years of support do not compete for available funds. Without this noncompeting moral commitment, instability would be introduced that would seriously endanger research progress. This procedure of instilling stability into the research environment has been a cornerstone of Federal research policy for some three decades.

A grant changes from noncompeting to competing status at the end of its originally approved project period. As I have indicated, that period may extend up through 5 years. At the end of that period that grant, if it is to be continued, must "compete" for renewal with similar grants and with "new" requests—those requesting original support of a particular project or activity—for available funds.

Traditionally, the NIH honors its noncompeting commitments on a preferential basis. This derives from the nature and reality of modern medical research. Without it the element of instability that would be introduced would seriously endanger research progress. Competing projects—whether new requests or renewals—are funded on a priority basis assigned in the scientific peer review process to the extent that funds are available.

SUPPORT FOR PRIORITY PROGRAMS

Mr. CONTE. Do you feel that this budget provides adequate support for the priorities which you and the Congress have established in this area?

Dr. RINGLER. No. While there are undoubtedly a great many things that need to be done, there is also the recognition that there must be overall government perspective and allocation of scarce resources. As I said, my personal view is that as long as I can have a hearing with the Department people about what the Institute share of the total package should be, then I think that is a reasonable way to deal with it.

POSITIONS

Mr. CONTE. Do you have enough positions under this budget to properly carry out your functions?

Dr. RINGLER. It is difficult to give a precise answer to the question. I believe that additional positions could certainly be well utilized. Our annual reports have indicated the need for about 800 positions, but those plans did not presume the tight budget we are now presenting.

PREDOCTORAL FELLOWSHIPS

Mr. CONTE. How will your programs be affected by the general phaseout of predoctoral fellowships?

Dr. RINGLER. While the NHLI does not support a predoctoral training program, the major support of which has come from NIGMS, to the extent that a good number of predoctorals eventually become postdoctoral fellows in heart, lung, and blood disciplines, a curtailment of support will have impact on our future research programs.

RESEARCH CONTRACTS

Mr. CONTE. What portion of your research is done on a contract as opposed to grant basis?

Dr. RINGLER. In fiscal year 1974 66 percent of NHLI research, excluding training, was funded by grants and 34 percent by contracts. The budgeted amounts are 69 percent for grants and 31 percent for

contracts in 1975 and 72 percent for grants and 28 percent for contracts in 1976.

Mr. CONTE. Do you have adequate resources to effectively oversee your contracted research programs? How might such oversight be improved?

Dr. RINGLER. We have experienced two major problems in contract management. One has been an inadequate number of staff to monitor the contracts. Another problem has been a restriction on travel that has militated against optimal overseeing of the technical work being conducted under contract. I do understand, however, that an adjustment has been made in the travel allocation that has provided some relief during the latter part of this year.

Mr. CONTE. Would you describe your review procedure for contract awards?

Dr. RINGLER. Proposals which are to be considered for award under a request for proposal must be received by the closing date specified in that solicitation. Within the NHLI, primary technical review is the responsibility of the Review Branch, Division of Extramural Affairs. Review panels are convened by this group to evaluate each offer received and to provide us with their advice regarding these proposals. Panels are generally composed of nongovernment consultants who are recognized experts in the particular scientific area in which contracts are to be let. These consultants are chosen by the review branch after discussions with the Program Division initiating the project. By utilizing this mechanism, we are assured high quality and objective peer review of each proposal reviewed and evaluated for possible award in our contracts program.

Proposals received in response to a specific Request for Proposal are competitively evaluated in accordance with the "evaluation criteria" listed in descending order of importance in each RFP. These criteria are specifically developed with regard to the requirements of every procurement, emphasizing those factors considered critical to contractor selection. They are prepared by NHLI scientific staff simultaneous with the preparation of the RFP's technical requirements. Established evaluation criteria serve as a standard against which all proposals are judged.

Technical and business instructions together with the evaluation criteria, encompassed within the RFP document, provide offerors with all the information required to prepare and submit comprehensive proposals in response to those needs advertised by the NHLI.

When evaluating the proposals reviewers identify proposals as either unacceptable or acceptable, establish a technical ranking, and assign each a score. Technical evaluators may further determine whether any proposal might be more favorably considered after clarifying information is provided by the offeror. The Institute will arrange for submission of clarifying data either in writing or by consultation.

At the completion of technical review, an evaluation report is prepared and maintained as a permanent record in the official files. This report contains a narrative statement relative to each offer stating its strengths and weaknesses, and identifying any qualifications which may bear upon the selection of sources for negotiation and award.

Specific technical reasons supporting a recommendation of disapproval regarding any proposal are included in this proposal review summary.

Within the NHLI a secondary review is performed by the programmatic division originating the RFP. Written advice furnished by the initial peer review panel is utilized fully by the group in their evaluation. Opinions and recommendations this body may have which differ from those of the initial review group are documented in writing and are included as a portion of the record for the procurement, thus becoming part of the official file. Although substantial differences of opinion are relatively rare, they do occur, and are given due consideration by Institute officials prior to concurrence and approval for negotiation and contract award.

A financial analysis is also performed at this point in the review process. Both technical personnel and contract specialists participate in performing best buy analysis for the Government. Each approved proposal is analyzed and a final recommended cost figure is determined by eliminating unnecessary items while reviewing an offeror's proposed budget. That final recommended cost figure is used as our target for purposes of negotiation.

Upon conclusion of secondary review, complete and comprehensive documentation regarding the solicitation is prepared. This package of information is forwarded for final Institute concurrence and approval.

At this point, those proposals identified as recommended for award are negotiated and form the basis for an NHLI project or scientific subprogram supported by contract.

Mr. CONTE. What percentage of your research contracts are for academic researchers, and what portion for commercial interests?

Dr. RINGLER. Approximately 80 percent of the number of our research contracts are awarded to academic or other nonprofit scientific institutions. About 20 percent go to commercial researchers. Some 10 percent of contract dollars are awarded to profit institutions.

Mr. MICHEL. Dr. Ringler, welcome to the committee.

I apologize for my absence during a good part of this particular hearing when we have been detained over on the floor with some of the other things going on.

We are obviously reading the record very carefully.

TOTAL FEDERAL COMMITMENT TO RESEARCH IN HEART, LUNG, AND BLOOD DISEASES

One of the things that interests me as we consider the work done in the various institutes of the NIH is the research done in the same field by other Government agencies.

For example, doesn't the AEC and the VA and others do some research in areas directly associated with the Heart and Lung Institute?

Dr. RINGLER. Yes, they do.

I have a report within the Institute I will be glad to make available to the committee that attempts to describe all the work supported by

the entire Federal Government related to heart, lung, and blood disease.

Mr. MICHEL. How extensive a thing is that?

Dr. RINGLER. We can give it to you in whatever level of detail you want. Just to give you a specific example, in a few charts and tables we can summarize the total federal initiative in this area.

Mr. MICHEL. Would you provide that for the record within reason? If some parties want to go into detail, just tell us what publication it is that you go into.

Dr. RINGLER. We can reference the publication in the record.

Mr. MICHEL. Are you aware of any other agencies in the Federal have a major emphasis one way or another related to heart, lung, and VA?

Dr. RINGLER. Yes, sir.

There are about 17 agencies within the Federal Government that have a major emphasis one way or another related to heart, lung, and blood problems.

Mr. MICHEL. Those will be enumerated in whatever you present?

Dr. RINGLER. Yes, sir.

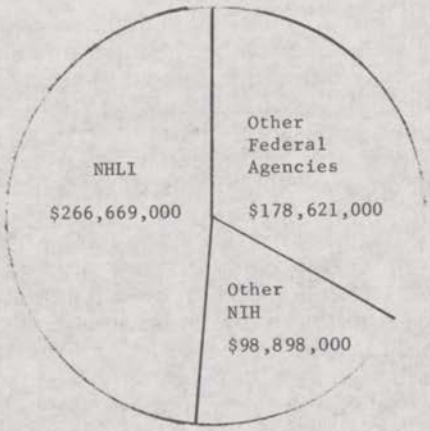
Mr. MICHEL. Do you know off hand what that overall figure was?

Dr. RINGLER. My memory is $536 million. That is from memory and may not be precisely right but it is in that order of magnitude.

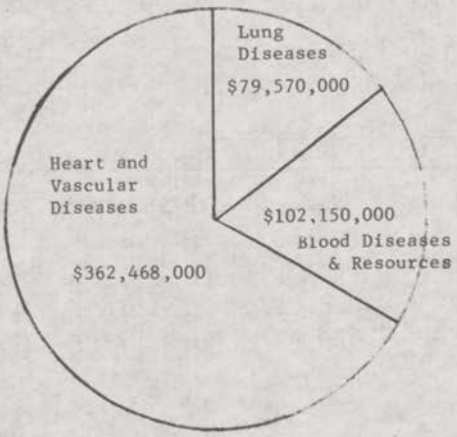
[The information follows:]

Overall Support By Federal Government Research
In Heart, Lung, and Blood Diseases

Data Summary -- FY 1974



Heart, Lung, and Blood Research Support Total =
$544,188,000*



*Not Final Figures -- Adjusted from Previous Totals of $536 million

U.S. GOVERNMENT SUPPORT FOR RESEARCH IN HEART, LUNG, AND BLOOD DISEASES

Funding Summary By Federal Department Agencies--FY 1974

	Amount
National Institutes of Health	
National Heart and Lung Institute (NHLI)	$266,669,000
National Cancer Institute (NCI)	11,980,000
National Eye Institute (NEI)	2,430,000
National Institute of Allergy and Infectious Diseases (NIAID)	13,671,000
National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD)	25,493,000
National Institute of Child Health and Human Development (NICHD)	6,830,000
National Institute of Dental Research (NIDR)	6,291,000
National Institute of Environmental Health Sciences (NIEHS)	3,781,000
National Institute of General Medical Sciences (NIGMS)	6,165,000
National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)	6,721,000
National Library of Medicine (NLM)	32,000
Division of Research Resources (DRR)	15,504,000
Subtotal, NIH	365,567,000
Other Agencies of the Department of Health, Education, and Welfare	
Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA)	2,245,000
Center for Disease Control (CDC)	4,318,000
Food and Drug Administration (FDA)	1,113,000
Health Resources Administration (HRA)	19,998,000
Health Services Administration (HSA)	105,057,000
Social and Rehabilitation Service (SRS)	1,885,000
Social Security Administration (SSA)	*
Subtotal, Other DHEW	134,616,000
Other Departments and Agencies	
Department of Agriculture (USDA)	1,046,000
Department of Defense (DOD)	3,606,000
Department of Transportation	11,375,000
Atomic Energy Commission (AEC)	14,535,000
Environmental Protection Agency (EPA)	6,392,000
National Aeronautics and Space Administration (NASA)	2,201,000
National Science Foundation (NSF)	4,850,000
Veterans Administration	*
Subtotal, Other Departments and Agencies	44,005,000
Total, U.S. Government Funding	544,188,000

Funding Summary for Major Research Program Areas

Major Program Areas	Program Funding			
	NHLI	Other NIH	Other DHEW and Federal Agencies	Total
Heart & Vascular Dis.	$178,725,000	$33,795,000	$149,948,000	$362,468,000
Lung Diseases	40,109,000	18,380,000	21,082,000	79,571,000
Blood Diseases & Resources	47,835,000	46,723,000	7,591,000	102,149,000
Total	266,669,000	98,898,000	178,621,000	544,188,000

*No Funding Available.

Comparable data for FY 1973 is published in:

National Heart, Blood Vessel, Lung, and Blood Program
First Annual Report of the Director of the National Heart and Lung Institute, February 13, 1974
U.S. Department of Health, Education, and Welfare, Public Health Service
National Institutes of Health, National Heart and Lung Institute
DHEW Publication No. (NIH) 74-514

National Heart, Blood Vessel, Lung, and Blood Program
Related Federally Supported Programs, FY 1973, Parts I and II, May 15, 1974
U.S. Department of Health, Education, and Welfare, Public Health Service
National Institutes of Health, National Heart and Lung Institute
DHEW Publication No. (NIH) 75-687

INCIDENCE OF ARTERIOSCLEROSIS IN THE U.S. COMPARED WITH OTHER COUNTRIES

Mr. MICHEL. In your justifications you say arteriosclerosis is the chief cause of death in the United States and is by far the most common disease affecting man in Western society. Do you have any statistics on the incidence of arteriosclerosis in other Western countries?

Dr. RINGLER. Yes.

We are unfortunately a leader if you will. Finland exceeds us a little. We have a very high incidence of coronary heart disease in this country. Countries like Sweden which is a highly developed industrial nation as you are well aware have a rate that is perhaps half of ours.

If your next question is going to be why, my answer is that I don't know. Some ideas have to do with the fact that they live a different life style over there. My personal judgment is that they eat somewhat less and exercise more than we do. Those are personal judgments and I could not document them from scientific literature.

Mr. MICHEL. I don't know that I should encourage or suggest that you have a grant for somebody to study that. But if you came up with the answer to that, maybe we could save ourselves a lot of research money in other areas if we just found the key to that one.

Dr. RINGLER. We have work underway in this area. We have tried to compare Japanese populations in Japan with Japanese populations which have moved to Hawaii, with Japanese populations that have moved to the United States comparing those to the United States and comparing those with people who live in Puerto Rico, to see if one can identify differences.

Those studies are ongoing. We will be undertaking a rather major analysis of them soon. At the moment I cannot summarize what they are likely to show.

Mr. MICHEL. Why in your testimony have you referred only to Western society?

Dr. RINGLER. That is an expression we use, I suspect in part because we do not have good data on the other countries. For example, we have almost no information in the Soviet Union just to cite a specific example or in other countries.

We do have information from Japan because we have projects ongoing with them.

But by and large we do not have as good epidemiological vital statistics from the other countries.

For that reason we mentioned Western countries because they are the only ones we know about.

Mr. MICHEL. Do we, through the World Health Organization, ask for those from the other countries?

Dr. RINGLER. I cannot give you a specific answer because I have never asked through that mechanism. We in the Institute have attempted to get public health data from some countries. We have not been terribly successful.

Dr. LAMONT-HAVERS. In the international sphere, a major problem is one of definition and word usage and what do the words mean. I think that while you can get an impression you really will not know. Some countries do not willingly give their vital statistics for various reasons. Sometimes they do not know themselves and at other times they are not very happy for other countries to know what is going on. Therefore, it is a definitional problem as well as an information exchange problem.

ARTERIOSCLEROSIS IN EARLY AGE GROUPS

Mr. MICHEL. When you spoke of arteriosclerosis beginning early in life and becoming manifested by middle age or later, how early?

What are you talking about there?

Dr. RINGLER. The study that is usually cited in response to that kind of a question has to do with autopsy studies done on Korean soldiers at whatever age those soldiers were, but certainly in the late teens or perhaps early 20's. There was, to everyone's surprise, a substantial amount of arteriosclerosis in that age groups.

Dr. LAMONT-HAVERS. It was 18 to 23, I believe.

Mr. MICHEL. If we had been able to determine that the disease does begin at a certain period of life, are we able to isolate the specific cause and determine what action might be taken by individuals and early in life to prevent the disease?

Dr. RINGLER. A major thrust of the program is to identify those etiological factors that cause the disease. We have many approaches to it but we do not have a forthright answer to your question.

There are many factors that probably enter into why and how the disease develops. Until we can sort them all out, we will not be able to reverse it.

MANIFESTATIONS OF HEART ATTACK AND STROKE

Mr. MICHEL. You suggest heart attack and stroke as two examples of manifestations. Then you go on to say that virtually all adult American males and postmenopausal women are afflicted to some degree. Since all these persons obviously do not suffer heart attacks or strokes, what are the lesser manifestations of the disease and what measurable effect does this have on the average person?

Dr. RINGLER. A considerable amount of involvement of the arteries supplying the heart muscle and in those arteries supplying the brain can be present without any symptoms or impairment of normal function. For example, a person may have no symptoms of angina pectoris even with more than 60 percent of the cross sectional area of a coronary artery being obstructed by a localized accumulation of atherosclerosis.

The amount of blood flow through such an artery can still be sufficient to supply the needs of the heart muscle in normal activity but symptoms of angina pectoris, that is, chest pain, feeling of tightness and construction, and sweating that disappear when exertion is reduced, could be produced when such a person increases the amount of physical activity. The electrocardiogram exercise treadmill test is a procedure that can bring out evidence of inadequate blood flow in the coronary arteries under strenuous exercise.

Likewise with cerebral arteries there may be no symptoms until the degree of blood flow is sufficiently restricted to cause inadequate oxygen to the brain tissues. The lesser manifestations of such impaired blood flow to the brain can be brief episodes of feeling faint, blurring of vision, dizziness, or passing out. More definite evidence of temporary obstruction of cerebral blood flow can be manifested as temporary double vision, difficulty in speech, or temporary weakness of an arm or leg. These manifestations are possible evidence of a more advanced predisposition to develop stroke and a thorough evaluation would be needed with the possibility that some form of therapy would be indicated.

HIGH BLOOD PRESSURE INCIDENCE

Mr. MICHEL. It is estimated that about one-half of those suffering from high blood pressure are probably unaware that they have it. What are some of the symptoms which could clue someone into the fact that they may have a problem and should have their blood pressure checked?

Dr. RINGLER. One of the major problems in controlling high blood pressure is that the mild and moderate forms of the disease which afflict most persons have virtually no symptoms. The very few which may occur are quite general—headaches, dizziness—but these are very nonspecific to the disease of hypertension, and may be caused by a wide variety of other conditions. There is only one definitive means of detecting high blood pressure, that is measurement of the blood pressure. Because there are rarely symptoms to prompt the sufferer, only a highly developed sense of awareness and concern for personal health can prompt our citizenry to take this action. It is for this reason that the educational activities related to high blood pressure are so important.

Mr. MICHEL. Does a regular medical check-up presently provide the best chances of discovering this problem before a serious complication results?

Dr. RINGLER. The answer to that question is clearly yes. We urge everyone to have regular medical check-ups, in which reading blood pressure is included. Less desirable substitutes for regular medical check-ups are available in some areas at certain times, such as at community sponsored blood pressure measurement clinics. But the importance of regular check-ups to determine blood pressure, as well as other health conditions, cannot be overstressed.

STROKE PROGRAMS

Mr. MICHEL. Though the specific emphasis of the stroke programs within your Institute and the Institute of Neurological Disease and Stroke—or I guess I should say Neurological and Communicative Disorders and Stroke, since we've changed the name, but even though the emphasis on stroke research differs, doesn't the research overlap to some extent? By what procedures are these programs coordinated?

Dr. RINGLER. The National Heart and Lung Institute has responsibility for disease changes that affect the blood and blood vessels that supply the brain—for example, blood clotting disorders, arterioscle-

rosis, and hypertension. The NINCDS has responsibility for the disease changes affecting the brain itself.

There is some overlap. It is mostly in the study of the actual circulation of the blood through the brain to nourish it. Most of the research on blood flow through the brain and its measurement and control is supported by the NINCDS.

Liaison is by staff contact between the two Institutes and by dual assignments of grant applications to the two Institutes in areas of potential overlap. In the larger aspects of coordination there has been a subcommittee drawn jointly from the advisory councils of the two Institutes and there has been the mutual use of some consultants on appropriate task forces. Both Institutes have participated in the support of the well-known Princeton Conferences on Cerebrovascular Disease, and in the development and dissemination of Cerebrovascular Bibliography, issued quarterly, which lists titles of articles selected from the National Library of Medicine's Index Medicus.

SEX DIFFERENCES IN MORTALITY FROM CORONARY HEART DISEASE

Mr. MICHEL. According to your justifications, coronary heart disease is the leading cause of death in men after age 38 and in women after age 55. Have you been able to make any conclusions regarding the disparity in the age factor between the sexes? Is there a particular reason for the 17-year reprieve for women?

Dr. RINGLER. It is well recognized that coronary heart disease incidence is lower in young women than young men but that with advancing age rates for women tend to approach those of men. The reasons for this are not known, but one factor clearly suspect is the different hormonal makeup of the two sexes.

One way to study the role of sex hormones on the atherogenic process is to examine the changes associated with menopause. Despite many such cross sectional investigations, particularly in respect to serum lipids, uncertainties remain. In an effort to ferret out possible explanations for those uncertainties, data from the Framingham Study were used to study the problem from a longitudinal point of view. Women from the Framingham cohort who were premenopausal at the initial examination and subsequently followed for the next 8 examinations were assessed in relation to a change in menopausal status on weight, systolic, and diastolic blood pressure, serum cholesterol, blood glucose, vital capacity, and hemoglobin. Of the characteristics assessed only two showed statistically significant changes. Serum cholesterol and hemoglobin rise with the onset of menopause. In the case of serum cholesterol this rise is clearly abrupt.

The small impact of menopause on the characteristics investigated may well underestimate the role of hormonal differences in delaying the onset of coronary heart disease in women as compared to men. The abrupt rise in serum cholesterol following menopause, while not large enough in itself to account for the acceleration in coronary heart disease in postmenopausal women, may signal some other as yet undetected change in lipid metabolism associated with hormonal deprivation.

HEART FAILURE

Mr. MICHEL. You define heart failure as occurring when the heart has been damaged so extensively that its ability to pump blood is impaired and it can no longer meet the needs of the body. Could you expand on the difference between this and other forms of heart disease? Isn't heart failure the extreme result of other heart ailments and wouldn't that disease be the actual cause of death?

Dr. RINGLER. Heart failure is a nonspecific term which implies that the heart is literally failing to perform the tasks that it is required to do.

It can be the end result of several different forms of heart disease such as infections in the valves of the heart, congenital abnormalities in the structure of the heart muscle or valves, rheumatic involvement of the heart valves, or destruction of the heart muscle as a result of too little blood flow as occurs in the case of obstructive coronary artery disease or "heart attack."

You are correct in assuming that heart failure is the extreme result of other heart ailments which could be ultimately responsible for a person's death.

ASPIRIN-MYOCARDIAL INFARCTION STUDY

Mr. MICHEL. In regard to the aspirin-myocardial infarction study, why has aspirin been chosen as a deterrent to this?

Dr. RINGLER. A few years ago an observation was made that it appeared that people who take aspirin routinely have fewer heart attacks than those who do not. Fundamentally it is as simple as that basic observation. It is called the Boston Drug Surveillance Study which follows the people who take various kinds of medication for various conditions. They observed that there was strong evidence that perhaps the people who take aspirin routinely have fewer heart attacks. We have looked into this and on the basis of a rather careful analysis of the situation feel that that hypothesis should be tested. It should be tested very soon because aspirin, as you are well aware, is freely available. If one is going to test it in a scientific way, you have to do it in a controlled fashion so that those on a placebo are on a placebo and those on aspirin take it. The basic observation is as I just indicated.

Mr. MICHEL. Rightly or wrongly, I always proceeded on the assumption that it is probably best not to take anything I don't have to, other than vitamins or some body-building element. You know you read this about the aspirin and the natural inclination would be, "Gosh, routinely every night before I go to bed I will take a couple of aspirin whether I need it or not." I am not sure whether someone is erroneously being taken down a bad path, but I think it would be appropriate to have a study.

Dr. RINGLER. We are undertaking such a study. It will begin in an active way very soon, about now, as a matter of fact. We will follow the patients for a 3-year period at the end of which time we hope to have a definitive answer to the question.

Mr. MICHEL. You don't hear so much anymore about transplants. In years past when this was all the talk, I had several tables submitted in the record of those survivors. I wonder if we might have that brought up to date, if that has not been asked for yet?

Dr. RINGLER. It has not. There have been 272 transplants and 46 survivors. We can submit the table for the record.

Mr. MICHEL. Fine. You feel free to expand in the record as to what the general feeling is with respect to transplants. I know many years ago when we were just in the infancy stage we talked about both approaches, transplants or artificial, and we felt we should go both ways and maybe later make a choice if that becomes critical at some future time.

Dr. RINGLER. Most of the transplants being done in this country are being done by one group. They are doing about one transplant a month. The period of survival is improving very substantially. We can cover a few of those points for the record.

Mr. MICHEL. Fine.

[The information follows:]

A REVIEW OF HUMAN SOLID ORGAN TRANSPLANTATION[1]

During 1973, 33 heart transplants were performed by 11 teams, 4 located in the United States, 3 in France and 1 each in Belgium, Canada, England, and South Africa. Eight of the thirty-three patients were alive (January, 1975) from 1 to 2 years after transplantation. Three others lived for 10, 13, and 18 months before dying of graft rejection and infectious complications. The team at Stanford (California) University is responsible for 15 of the 33 transplants and 6 of the 8 patients surviving the 1973 surgery are Stanford patients.

Twenty-seven heart transplants were reported to the registry in 1974. Only Shumway and Lower in the United States were active, though six other teams participated worldwide. Seven cases were done in France and teams in Australia, Belgium, and South Africa reported one case each. At the end of 1974, the registry had recorded a total of 263 heart transplants in 257 patients; 44 were alive. The number of recipients that had survived 1, 3, 5, and 6 years was 55, 21, 9 and 5 respectively. On January 1, 1975, three recipients were alive and well more than 6 years after transplantation. Three long-term survivors died during 1974. They were: Louis B. Russell, Jr. (6 years, 3 months); Dusan Vlaco (6 years, 2 months); and Ralph Trout, the longest survivor in the Stanford series (5 years, 4 months). Of course, the biggest heart transplant news came from South Africa where Barnard's team performed two auxiliary grafts with survival of both recipients.

[1] Bulletin of the American College of Surgeons.

ACS / NIH ORGAN TRANSPLANT REGISTRY

55 EAST ERIE STREET • CHICAGO, ILLINOIS 60611 • Area 312/664-4050

UPDATE ON ORGAN TRANSPLANTATION IN THE WORLD	HEART	LIVER	LUNG	PANCREAS	KIDNEY
Transplant teams	64	40	21	13	293
Transplants	272	236	36	39	20,900
Recipients	266	227	36	39	18,785
Alive with functioning grafts	46	22	0	2	approx. 8,500
Longest survival with functioning graft	6.4 yr	5.7 yr	10 mo	2.8 yr	19 yr*
Longest current survival with functioning graft	6.4 yr	5.7 yr	---	2.8 yr	19 yr
Cases reported to the Registry, April 1, 1975					

*Identical twin transplant

WORLD TOTALS AND CHRONOLOGY OF ORGAN TRANSPLANTATION

YEAR	HEART	LIVER	LUNG	PANCREAS	KIDNEY
1953-1961					123
1962					67
1963		6	2		157
1964		4	0		359
1965		7	3		453
1966		3	1	2	560
1967	2	8	6	1	831
1968	101	39	6	6	1,243
1969	47	46	7	7	1,535
1970	17	31	2	9	1,987
1971	18	15	4	1	2,933
1972	18	23	3	4	3,465
1973	33	24	2	4	3,783
1974	29	27	0	3	3,032
1975	7	3	0	2	212
Total	272	236	36	39	20,900

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HUMAN HEART TRANSPLANTATION

Dec 3, 1967 - April 1, 1975

World Totals . 22 Countries

Transplant teams	64
Transplants	272
Recipients	266
Living recipients	46

Chronology and World Distribution . April 1, 1975 *
(numbers in parentheses indicate survivors)

Year	World Totals	U.S.A.	Canada	France	South Africa	Other Countries**
1967	2	1	0	0	1	0
1968	101 (3)	54 (1)	14 (1)	10 (1)	2	21
1969	47 (2)	34 (1)	1	0	4 (1)	8
1970	17 (4)	16 (4)	1	0	0	0
1971	18 (4)	13 (3)	1	0	3 (1)	1
1972	18 (5)	15 (5)	0	0	2	1
1973	33 (7)	21 (6)	1	8 (1)	1	2
1974	29 (15)	17 (10)	0	9 (3)	1 (1)	2 (1)
1975*	7 (6)	4 (4)	0	1	1 (1)	1 (1)
Total	272 (46)	175 (34)	18 (1)	28 (5)	15 (4)	36 (2)

**Argentina, Australia, Belgium, Brazil, Chile, Czechoslovakia, England, Germany, India, Israel, Japan, Peru, Poland, Spain, Switzerland, Turkey, USSR, Venezuela.

Surviving Recipients of Human Heart Transplantation — April 1, 1975

	Date of Transplant	Survival time	Transplant Team
1)	10/21/68	6 yr 5 mo	Lepley, St. Luke's Hospital, Milwaukee
2)	11/17/68	6 yr 4 mo	Baker, St. Michael's Hospital, Toronto
3)	11/28/68	6 yr 4 mo	Henry, Centre Cantini, Marseille, France
4)	04/17/69	5 yr 11 mo	Barnard, Groote Schuur, Cape Town, So. Africa
5)	08/13/69	5 yr 7 mo	Roe, University of California, San Francisco
6)	01/03/70	5 yr 3 mo	Shumway, Stanford University, Stanford, Calif.
7)	01/16/70	5 yr 2 mo	Shumway
8)	07/04/70	4 yr 9 mo	Shumway
9)	10/15/70	4 yr 5 mo	Shumway
10)	03/22/71	4 yr ----	Shumway
11)	05/10/71	3 yr 10 mo	Barnard
12)	11/08/71	3 yr 4 mo	Shumway
13)	12/15/71	3 yr 3 mo	Shumway
14)	01/07/72	3 yr 3 mo	Shumway
15)	06/10/72	2 yr 10 mo	Shumway
16)	08/20/72	2 yr 7 mo	Shumway
17)	11/19/72	2 yr 4 mo	Shumway
18)	12/31/72	2 yr 3 mo	Shumway
19)	01/11/73	2 yr 2 mo	Lower, Medical College of Virginia, Richmond
20)	03/08/73	2 yr 1 mo	Shumway
21)	04/27/73	1 yr 11 mo	Shumway
22)	06/09/73	1 yr 10 mo	Guilmet, CMC Foch Hospital, Suresnes, France
23)	08/07/73	1 yr 8 mo	Shumway
24)	10/10/73	1 yr 5 mo	Shumway
25)	12/12/73	1 yr 3 mo	Shumway
26)	02/22/74	1 yr 1 mo	Primo, Brugmann Hospital, Brussels, Belgium
27)	03/12/74	1 yr ----	Cabrol, Hopital de la Pitie, Paris, France
28)	03/31/74	1 yr ----	Shumway
29)	05/11/74	10 mo	Shumway
30)	06/21/74	9 mo	Shumway
31)	07/31/74	8 mo	Shumway
32)	08/19/74	7 mo	Shumway
33)	08/25/74	7 mo	Shumway
34)	08/30/74	7 mo	Shumway
35)	09/07/74	6 mo	Cabrol
36)	10/19/74	5 mo	Shumway
37)	11/16/74	4 mo	Shumway
38)	11/21/74	4 mo	Lower
39)	11/25/74	4 mo	Barnard
40)	12/15/74	3 mo	Cabrol
41)	01/01/75	3 mo	Barnard
42)	01/06/75	3 mo	Shumway
43)	01/25/75	2 mo	Shumway
44)	01/26/75	2 mo	Shumway
45)	01/30/75	2 mo	Primo
46)	02/24/75	1 mo	Shumway

Mr. MICHEL. How much money is in this budget for cystic fibrosis?

Dr. LAMONT-HAVERS. That will come up tomorrow, sir.

Mr. MICHEL. Thank you very much.

INSTITUTE SALARY SUPPORT AND PERSONNEL COMPOSITION

Mr. ROYBAL. I have one additional question.

I would like to have you submit for the record the money spent on salaries alone, the number of personnel you have and the ethnic composition of that personnel.

Dr. RINGLER. Within the Institute?

Mr. ROYBAL. Yes, only within the Institute's staff.

Dr. RINGLER. Fine.

Mr. ROYBAL. I would also like to have the classification of the work that they do, including their salary level. I'm primarily interested in knowing how many members of minority groups you have in your employ and how many have Spanish surnames.

Dr. RINGLER. We will see how we are doing.

Mr. ROYBAL. Thank you very much.

[The information follows:]

National Heart and Lung Institute
Salaries and Personnel

	1974	1975	1976
Obligations for salaries	$12,237,048	$14,585,000	$15,106,000
Permanent budgeted positions	700	711	691
Full-time equivalent of all other positions	80	80	80

Minority Employment
April 1, 1975

	No. Employees	Civil Service (GS) Average Grade	Work Area
Asian American	9	GS 9.1	Administration, intramural laboratory and clinical research, research grant and contract management.
Spanish Surname	9	GS 7.1	Administration, intramural laboratory and clinical research, research grant and contract management.
Blacks	27	GS 8.5	Administration.
	82	GS 6.5	Intramural laboratory and clinical research.
	12	GS 8.5	Research grant and contract management.

The mission of the National Heart and Lung Institute is to provide leadership for a National Program in diseases of the heart, blood vessels, lungs, and blood; plans, conducts, fosters, and supports an integrated and coordinated program of research, investigations, clinical trials, and demonstrations relating to the causes, prevention, methods of diagnosis, and treatment of these diseases through research performed in its own laboratories and through contracts and research grants to scientific institutions.

The NHLI does not have personnel to conduct community demonstrations. It cannot assign personnel to individual communities. The Institute staff formulates, coordinates, and reviews programs that can serve as models in the categorical disease approaches within the Institute's relevant program areas. The NHLI provides funding for these programs through research grants, research and development contracts, and in its National Research and Demonstration Center (funded through grants). While not intended to fund health care delivery per se, they provide support for the manpower necessary for coordination, educational opportunities, and the preparation and dissemination of educational or informational materials.

INSTITUTE REPORTS

Mr. STOKES. I have one further question. Dr. Ringler, in the first paragraph of your testimony you make reference to two reports. You say they have been submitted. Then you further say, "In my comments here I would like to summarize a few highlights from these reports." I was a little curious because I wanted further detail from the reports and I have just had the staff check and they inform me that neither report has been filed with the Congress as provided for in law.

I didn't know whether you were aware of that or not.

Dr. RINGLER. I am aware of that. The two reports are reports required by the law that is cited here, 92–423, one by the National Advisory Heart and Lung Council and the other by the Director of the Institute.

The Council's report is supposed to be forwarded, by the Council, that is, by the end of January and it has been forwarded. It is working its way through the executive branch now and my understanding is that it is somewhere between the Secretary's office and the White House.

The Institute's report is prepared after having obtained the advice and the input from the Council. The final draft of that is on my desk right now and it will leave there very soon and again it will be forwarded up through the normal channels, I guess is the way we say it.

Mr. STOKES. It sounds as if some of your work is something like some of our work.

Dr. RINGLER. Well, the law in the case of the Director's report does not specify a date. It does say send it as early as possible.

Mr. STOKES. One makes reference to the end of the calendar year and the other is January 31.

Dr. RINGLER. On the Director's report it says as soon as possible after the end of the calendar year. This is a fairly comprehensive report. It deals with a rather broad area. We try to do it well. It takes us a little while. I am not trying to make excuses.

Mr. STOKES. I can understand.

I just wanted to express my interest and concern about the full reports and as long as you say they are forthcoming that satisfies me.

Dr. RINGLER. Thank you.

Mr. STOKES. I have nothing further, Mr. Chairman.

Thank you.

JUSTIFICATION OF THE BUDGET ESTIMATES

Appropriation Estimate

NATIONAL HEART AND LUNG INSTITUTE

For expenses, not otherwise provided for, necessary to carry out title IV, parts B and I, and title XI of the Public Health Service Act, [$324,130,000] $292,794,000.

For the National Heart and Lung Institute for the period July 1, 1976 through September 30, 1976, $59,715,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

NATIONAL HEART AND LUNG INSTITUTE

Amounts Available for Obligation [1]

	1975 Estimate [2]	1976 Estimate
Appropriation	$324,130,000	$292,794,000
Comparative transfers to:		
"Research Resources" (for Rhesus monkey supply activities)	-98,000	
"Office of the Director, NIH" (Transfer of public affairs activities)	-37,000	
"Office of the Director, NIH" (Transfer of the Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	-111,000	
Total obligations	323,884,000	292,794,000

[1] Excludes the following amounts for reimbursable activities carried out by this account: 1975 $10,000; 1976 $10,000.

[2] Excludes 1973 restorations in the amount of $3,227,000.

Summary of Changes

1975 Estimated obligations	$323,884,000
1976 Estimated obligations	292,794,000
Net change	-31,090,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Within grade pay increases..	---	---	---	+ $200,000
2. Annualization of 1975 pay raise costs in 1976.....	---	---	---	+ 345,000
3. Extra day of pay.....	---	---	---	+ 35,000
4. Federal Telecommunications System (FTS) rate increases.	---	---	---	+ 22,000
5. Postage rate increase.....	---	---	---	+ 12,000
6. Bureau of Employment Compensation (BEC) rate increase..	---	---	---	+ 6,000
7. Payment ot the NIH Management Fund.....	---	---	---	+ 858,000
Subtotal.....	---	---	---	+1,478,000
B. Program:				
1. Research grants:				
a. Noncompeting continuations	---	$121,761,000	---	+35,711,000
b. Competing (new continuations & supplementals)..	---	---	---	+35,871,000
2. Fellowships.....	---	8,015,000	---	+ 2,400,000
Subtotal.....	---	---	---	+73,982,000
Total, increases.....	---	---	---	+75,460,000
Decreases:				
A. Program:				
1. Research grants:				
a. Noncompeting completed or converted to competing status.....	---	---	---	-32,472,000
b. Competing, completed, converted to noncompeting	---	---	---	-52,968,000
c. Special programs.....	---	6,000,000	---	- 1,136,000
2. Training grants.....	---	13,100,000	---	- 2,561,000
3. Laboratory & Clinical Research.....	387	24,383,000	-17	- 478,000
4. Research and Development Contracts.....	---	80,528,000	---	-16,700,000
5. Research Management and Program Services.....	324	17,129,000	-3	- 235,000
Total, decreases.....			-20	-106,550,000
Total, net change.....			-20	-31,090,000

Explanation of Changes

Increases:

A. Built-in: The increases will provide: 1. $200,000 for within grade increases ($110,000 in Laboratory and Clinical Research and $90,000 in Research Management and Program Services); 2. $345,000 for the annualization of 1975 pay raise costs in 1976 ($190,000 in Laboratory and Clinical Research and $155,000 in Research Management and Program Services); 3. $35,000 for one extra day of pay in 1976 over 1975 ($20,000 in Laboratory and Clinical Research and $15,000 in Research Management and Program Services); 4. $22,000 for increases in Federal Telecommunications System (FTS) rates (in Research Management and Program Services); 5. $12.000 for postage rate increases (in Research Management and Program Services); 6. $6,000 for increases in Bureau of Employment Compensation (BEC) rates ($3,000 in Laboratory and Clinical Research and $3,000 in Research Management and Program Services); 7. $858,000 for increased costs of the NIH Management Fund for centrally furnished services ($471,000 in Laboratory and Clinical Research and $387,000 in Research Management and Program Services).

B. Program:

1. Research grants:
   A. The amount of $35,711,000 in noncompeting continuations represents the new and renewal grants of high priority made in 1975 which will become noncompeting in 1976. Moral commitments of lower priority noncompeting grants will not be funded.

   B. The amount of $35,871,000 in competing research grants reflects: 1) $9,000,000 for new awards; 2) $24,071,000 for competing continuations; and 3) $2,800,000 in supplementals.

2. Fellowships: The increase of $2,400,000 will provide expansion for the National Research Service Award Program.

Decreases:

A. Program:

1. Research grants:

   a. The amount of $32,472,000 in noncompeting continuations represents noncompeting regular research grants that were completed in 1975 or that are being converted to competing status in 1976.

   b. The amount of $52,968,000 reflects the completion or conversion of competing grants in 1975 to a noncompeting status in 1976.

   c. The decrease of $1,136,000 in special programs represents lower funding for the Research Career Program and essentially stable funds for the phase-out of the Heart Cooperative Drug Study.

2. Training grants: The decrease of $2,561,000 in 1976 represents a phase-out of this program, which is being replaced by the National Research Service Awards.

3. Laboratory and Clinical Research: The program decrease of $478,000 and 22 positions represents the reduction of personnel and administrative costs and reduction in laboratory supplies and equipment necessary in order to find "built-in" increases not provided for elsewhere.

4. Research and Development Contracts: The decrease of $16,700,000 will result in fewer contracts and contracts with reduced work-scopes in the areas of heart and vascular diseases, lung diseases, and blood diseases and resources.

5. Research Management and Program Services: The program decrease of $478,000 and 22 positions represents the reduction of personnel and administrative costs, and reductions in laboratory supplies and equipment necessary in order to find "built-in" increases not provided for elsewhere.

Obligations by Activity

Page Ref.		1975 Estimate		1976 Estimate		Increase or Decrease	
		Pos.	Amount	Pos.	Amount	Pos.	Amount
79	Heart and vascular diseases.....	---	$187,777,000	---	$166,578,000	---	-$21,199,000
91	Lung diseases.....	---	44,615,000	---	39,589,000	---	-5,026,000
97	Blood diseases and resources.....	---	49,980,000	---	44,350,000	---	-5,630,000
106	Intramural laboratory and clinical research.....	387	24,383,000	370	24,699,000	-17	+316,000
110	Research management and program services.....	324	17,129,000	321	17,578,000	-3	+449,000
	Total obligations.	711	323,884,000	691	292,794,000	-20	-31,090,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	711	691	-20
Full-time equivalent of all other positions	80	80	---
Average number of all employees	774	754	-20
Personnel compensation:			
Permanent positions	$13,155,000	$13,531,000	+ $376,000
Positions other than permanent	1,000,000	1,100,000	+ 100,000
Other personnel compensation	430,000	475,000	+ 45,000
Subtotal, personnel compensation	14,585,000	15,106,000	+ 521,000
Personnel benefits	1,658,000	1,705,000	+ 47,000
Travel and transportation of persons	786,000	751,000	- 35,000
Transportation of things	100,000	100,000	---
Rent, communications, and utilities	800,000	800,000	---
Printing and reproduction	550,000	550,000	---
Other services:			
Project contracts	80,528,000	63,828,000	-16,700,000
NIH Management Fund	12,711,000	13,569,000	+ 858,000
Other	5,422,000	5,096,000	- 326,000
Supplies and materials	3,800,000	3,700,000	- 100,000
Equipment	1,100,000	900,000	- 200,000
Grants, subsidies, and contributions	201,844,000	186,689,000	-15,155,000
Total, obligations by object	323,884,000	292,794,000	-31,090,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action to be taken
1975 House Report	
1. The Committee believed that high priority should be given to pulmonary training programs. (Page 27)	1. The NHLI supports pulmonary training and development of researchers through Graduate Training Grants, Fellowships, Pulmonary Academic Awards, and Pulmonary Young Investigator Awards, a program in 1974. Funding for these programs will continue at slightly higher levels in 1976 over 1975.
2. The Committee felt that particular emphasis should be given to the programs in Blood Diseases and Resources. (Page 27)	2. This activity is estimated at $44,350,000 in 1976. Emphasis will will be placed in all the major problem areas: Bleeding and Clotting Disorders, Biomaterials, Sickle Cell Disease and Other Disorders of the Red Blood Cell, and Blood Resources.
3. The Committee noted the late submission of the annual reports of the Director of the Institute, as well as that of the National Heart and Lung Advisory Council. The Committee believes in timely submission of these reports in order that they can be used during the appropriation hearings. (Pages 27 and 28)	3. The NHLI is working with the Department to assure timely submission of these reports.
1975 Senate Report	
1. In view of the known risk factors for coronary artery disease and heart attacks, the Committee believes in intensified efforts to find out to what extent changes in life style and habits can reduce or prevent heart attacks. (Page 44)	1. The purpose of the Multiple Risk Factor Intervention Trial (MRFIT) is to determine whether or not a preventive program directed at reduction or elimination of risk factors (high cholesterol, high blood pressure, smoking) will result in a significant reduction in coronary heart disease deaths. Already, over 6,000 men, aged 35-37 with increased risk have been enrolled in this study, which is taking place at 20 centers throughout the country. An enrollment goal of 12,000 is expected to be reached during calendar 1975.

1975 Senate Report (Continued)

2. The Committee recommended that in order to facilitate the application of research findings to the prevention and control of heart and lung disease, a minimum of Ten Research and Demonstration Centers should be established, at least one in each HEW region. (Page 44)	2. At current funding levels, three Research and Demonstration (R&D) Centers will be funded, one in Heart and Vascular Diseases, one in Lung Diseases and one in Blood Diseases and Resources. In addition, prevention and control programs apart from these R&D Centers will be funded in excess of $15 million in 1975.
3. The Committee expressed concern over the continuing large number of deaths from heart attacks which occur before hospitalization, and directed that a portion of the increase over the House allowance be utilized for a program of providing emergency medical services. (Page 45)	3. Subsequent to the 1974 Appropriations Bill, $3,000,000 was transferred to the Health Services Administration for this activity. Research at NHLI on preventive measures and drug therapy complements the service aspects of this activity.
4. The Committee noted the need for research efforts against ischemic heart disease, and recommended a program of Ischemic Heart Disease Centers, to be launched in 1975. (Page 45)	4. The Specialized Centers of Research (SCOR) on Ischemic Heart Disease program is being implemented in 1975 with the award of nine center grants, where multidisciplinary clinical and fundamental research is directed at the reduction of death and disability from all forms of ischemic heart disease and to techniques of rehabilitation and problems of sudden cardiac death.
5. The Committee urged a more intensive effort in the National High Blood Pressure Education Program, and directed the further research in the area of hypertension and minorities. (Page 45)	5. This program is now fully operational. The second annual National High Blood Pressure Month, May, 1975, involves over 100 national organizations. The dangers of undetected and untreated hypertension has been told to the American public through thousands of newspaper and magazine articles, and free TV and radio broadcast advertising equivalent to several million dollars.
6. The Committee recommended that the NHLI program on hemophilia be expanded. (Page 46)	6. Expanded hemophilia research is progressing toward the objective of better understanding of the mechanisms affecting hemostasis (arresting the flow of blood), improved understanding of the genetic mechanisms, development of better diagnostic tests, more effective therapy and an improved quality of life for the hemophiliac and his family.

1975 Senate Report (Continued)

7. The Committee recommended that up to $25 million be alloted for an expanded program in Sickle Cell Disease. (Pages 46 and 47)	7. This program was funded at over $16,000,000 in 1974, consisting of research grants and contracts, comprehensive centers, and screening and education clinics. These clinics, administered by the Health Services Administration, screened some 400,000 people for evidence of sickle cell disease. At the proposed budget for 1976, the program will remain at approximately the $16,000,000 level.
8. The Committee directed that the NHLI continue the taste and smell clinic at the 1973 level, and that a report on the activities and plans for this program be submitted within two months following enactment of the appropriations bill. (Page 47)	8. During the year, the Assistant Secretary for Health notified the Committee Chairman that, after a thorough review of this program by a committee of NIH clinical investigators, who found no substantial basis for continuation, the programs would be terminated. Patients would be referred back to their private physicians, who would be given a complete account of the findings and treatment for each patient at the clinic.
9. The Committee noted that lack of progress in the prevention and control programs and research and demonstration centers, and directed that additional funds and positions be provided to carry them out. (Page 47)	9. Three research and demonstration centers have been established in 1975. One with major emphasis in heart and vascular diseases (in Texas), another emphasizing lung diseases (in Vermont), and in blood diseases and resources (state of Washington). Control programs, including the Hypertension Detection and Follow-Up Program, Lung Disease educational programs, and control programs in sickle cell disease will be funded in 1976 at approximately $18.7 million.

Authorizing Legislation

Legislation	1976 Authorized	1976 Appropriation Requested
Public Health Service Act Title III, Part A, Section 301--Research and Investigation, In General	Indefinite	
Title IV, Part B--National Heart and Lung Institute	1/	$271,840,000 3/
Title IV, Part I--National Research Service Awards	2/	20,954,000 3/

1/ Authorization expires June 30, 1975.

2/ Authorization expires June 30, 1975. Extension legislation is proposed.

3/ Funding estimate only.

National Heart and Lung Institute
Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$133,235,000	$138,035,000	$135,385,000	$133,429,000
1967	139,147,000	145,827,000	155,827,000	155,827,000
1968	157,846,000	157,846,000	165,255,000	157,817,000
1969	160,310,000	154,695,000	162,695,000	157,502,500
1970	151,088,000	151,088,000	171,526,000	161,831,500
1971	164,923,000	169,207,000	194,207,000	186,798,000
1972	188,225,000	203,299,000	243,299,000	224,302,000
1973	246,829,000	290,538,000	340,538,000	290,538,000 1/
1974	264,754,000	281,754,000	319,754,000	286,749,000 2/
1975	309,053,000	320,950,000	329,754,000	323,884,000
1976	292,794,000			

1/ This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

National Heart and Lung Institute
Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$141,412,000	$146,212,000	$143,462,000	$141,462,000
1967	148,407,000	154,770,000	169,770,000	164,770,000
1968	167,954,000	167,954,000	177,954,000	167,954,000
1969	169,735,000	164,120,000	172,120,000	166,927,500
1970	160,513,000	160,513,000	182,000,000	171,377,500
1971	171,747,000	178,479,000	203,479,000	194,925,000
1972	195,492,000	211,624,000	252,590,000	232,627,000
1973	255,280,000	300,000,000	350,000,000	300,000,000 1/
1974	265,000,000	281,415,000	320,000,000	289,550,000 2/
1975	309,299,000	321,196,000	330,000,000	324,130,000
1976	292,794,000			

1/ This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/Appropriation after reduction.

Justification

- National Heart and Lung Institute

Authorizing Legislation: Public Health Service Act: Title III, Part A, Section 301, Research and Investigation, in General; Title IV, Part B--National Heart and Lung Institute, and Title XI, Genetic Blood Disorders. Authorization expires June 30, 1975.

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	711	$15,901,000	691	$16,811,000	-20	+$910,000
Other expenses	--	307,983,000	--	275,983,000	--	32,000,000
Total	711	323,884,000	691	292,794,000	-20	-31,090,000

General Statement

The research programs supported by the National Heart and Lung Institute have potential value for every citizen in our country. They deal with diseases that affect all age groups, both men and women, all ethnic groups, and all strata of our society. More than 30 million Americans suffer from these diseases, the annual economic costs resulting from heart, lung, and blood diseases are in excess of $40 billion, and heart disease alone is responsible for more deaths than all other causes combined.

It was in recognition of the magnitude of these disease problems and the potential for their solution that the National Heart, Blood Vessel, Lung, and Blood Act (P.L. 92-423) was enacted in 1972 and a National Program against these diseases was initiated.

The National Program provides a frame-work for collaboration between scientists, in determining the underlying causes and means of managing these diseases, and the public, in controlling environmental factors and personal habits that may increase the risk of these diseases. Because of the present and potential ability to control and cure the diseases involved, the Program could have an enormous impact on the nation's health.

The National Heart and Lung Institute and the scientific community it represents can provide a combination of vital factors needed for the achievement of the goals of the Program. They can provide almost three decades of experience, extensive research expertise, long established stability, highly trained and capable manpower, and an extensive pool of knowledge. During the past two years, the Institute and the scientific community have made rapid progress to meet the challenges and carry out the responsibilities presented in the 1972 legislation.

The passage of the Act significantly expanded the Institute's mandate and responsibilities. To implement the new and increased activities authorized by the Act in an efficient and timely manner, the Institute made significant changes in its organizational structure, program management, and ways of communicating and collaborating with the public and the professional communities. The Institute was reorganized into five divisions. Three of these are categorical divisions: Division of Heart and Vascular Diseases, Division of Lung Diseases, and Division of Blood Diseases and Resources. The other two are the Division of Extramural Affairs and the Division of Intramural Research.

An Office of Prevention, Control, and Education has been established in accordance with the Act. Through this office and through its categorical program divisions, the Institute began to implement the prevention, control, and education programs provided for in the Act. In FY 1975 the Institute initiated three National Research and Demonstration Centers--one in each of the three categorical areas--in accordance with the provisions in the Act. The legislation considerably expanded the National Heart and Lung Advisory Council, both in its membership and in its responsibilities. In addition to its duties of reviewing and recommending approval of applications for research funds, the Council now plays an active role in the development, review, and evaluation of the National Program. Through a number of collaborative efforts with other institutes, agencies, and organizations, and through the Interagency Committee mandated by the Act, the Institute has sought more effectively to utilize the national resources available for the National Program.

Some of the other new activities which have been initiated since passage of the Act and which have significantly added to the Institute's responsibilities are:

- Development of an expanded program in lung diseases.
- Coordination of the National Sickle Cell Disease Program.
- Coordination of the National High Blood Pressure Education Program.
- Launching of the National Blood Policy efforts.
- Implementation of several large-scale clinical trials in arteriosclerosis hypertension, and myocardial infarction, involving hundreds of thousands of individuals across the nation.
- Annual updating of the 5-year National Program Plan and the development of an annual report to the President and the Congress.

Impact of the National Program

The National Program is just beginning its third year. As the program continues, more and more information will accumulate on progress in basic research, clinical investigations, and clinical trials. Health care applications of the results of the program will also become available. The following paragraphs describe selected areas in which progress over the first two years of the program has been significant enough to warrant descriptions of cumulative impact or early trends of the program. This initial presentation on the impact of the Program focuses on those communities and institutions currently being served by the National Program. This information is provided as an initial indication of the degree to which the National Program can be of significant benefit to various segments of the American public. Currently benefiting from the National Program are the general public, high-risk populations, the black population, medical practitioners, research scientists, and the nation as a whole.

The General Public

Through a campaign to increase awareness of high blood pressure and its consequences, the American people are being encouraged to avail themselves of high blood pressure detection, diagnosis, and, where required, treatment. This campaign has been and is being accomplished through the National High Blood Pressure Education Program.

To date, this Program has involved active support of approximately 60 major national organizations and/or industrial groups, 48 state health depart-

ments, and numerous local community organizations. A significant degree of coordination has been developed both within the Federal Government and the private sector as exemplified by these selected items:

- Successful launching of National High Blood Pressure Month during May 1974.
- Development and promulgation of nationally recognized standards for screening, evaluation, therapy, and education of hypertensive patients.
- Development and operation of a Community Consultation Service which has assisted over 175 communities.
- Development and operation of a High Blood Pressure Information Center which has responded to over 550,000 requests.
- Development and operation of an ongoing mass media education campaign which has presented educational messages to an estimated 75 percent of the nation's population.
- Development and operation of an ongoing cooperative professional education effort designed to reach physicians, nurses, dentists, pharmacists, and other health personnel, and including development and promulgation of performance characteristics for physicians engaged in detecting and treating high blood pressure.

High Risk Populations

More than 160,000 men and women between the ages of 30-69 in 14 communities have been screened for hypertension under such programs as the Hypertension Detection and Follow-Up Program. The 11,400 persons found to have high blood pressure in this program are enrolled in a five-year follow-up study to determine the extent to which mortality can be reduced by sustained blood pressure treatment.

Another preventive program directed at persons who are at risk of developing coronary heart disease has been undertaken in the Multiple Risk Factor Intervention Trial (MRFIT). By the end of calendar 1974, in excess of 127,000 males, aged 35-57, had been screened and 4,600 accepted into the MRFIT program. Also, those who were not accepted for the trial but who exhibited cardiovascular disease symptoms were referred for diagnosis and treatment. It is anticipated that, in order to achieve the population of 12,000 necessary for the MRFIT study, in excess of 400,000 men will eventually have been screened at the 20 facilities throughout the country participating in the MRFIT program.

The Black Population

A sizeable portion of the nation's black population is receiving screening and counseling services concerning sickle cell disease in 26 Sickle Cell Screening and Education Clinics and in 15 Comprehensive Sickle Cell Disease Centers throughout the country. The purpose of these clinics, which are funded by the Institute and administered by the Health Services Administration, is to serve as a model to determine methods of carrying out service activities such as public awareness, education, screening, counseling, and patient referral under various circumstances in a variety of environments. By the end of calendar 1974, more than 700,000 persons had been served by these clinics.

Medical Practitioners

Improvements in research and clinical capabilities at many hospitals around the country are being made as a part of research and prevention, control, and education efforts being sponsored at those institutions under the National Program. This, in turn, increases the capabilities of the medical practitioners responsible for patient care in these institutions.

Research Scientists

A wide range and number of biomedical scientists in many disciplines are being supported under the National Program to obtain the fundamental knowledge necessary to mount the national attack against heart, blood vessel, lung, and blood diseases and to improve the national blood resources. For examples, as of 1974, the Institute was supporting the biomedical and clinical research activities of 2,400 principal investigators.

Nation As A Whole

The recently initiated National Research and Demonstration Centers in heart, blood vessel, lung, and blood diseases will serve as research and clinical focal points in their respective geographic areas. Three such Centers, one in each of heart and blood vessel diseases, lung diseases, and blood diseases and blood resources are being established in 1975. As these centers continue to develop, they will serve to train additional personnel and to educate the public in the geographic areas which they serve.

Summary

Through these representative examples of types of activities being supported by the National Program, it can be seen that, in its short history, the National Program has already reached large segments of the American population. It has helped to improve the recognition of heart, blood vessel, lung, and blood diseases and to provide avenues for better diagnosis and treatment. Further, advanced health care has been provided as a by-product of clinical studies such as the Multiple Risk Factor Intervention Trial, the Hypertension Detection and Follow-Up Program, and Lipid Research Clinics. Also, health research, health care, and health field personnel and facilities are being upgraded through the National Program. Finally, the establishment of the initial National Research and Demonstration Centers initiates a program which is expected to further improve medical capabilities and services throughout the country.

DHEW - National Institutes of Health

CROSSWALK - 1975 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Heart and Lung Institute
(Dollars in thousands)

Program	Research Grants: Regular Program: Non-competing	Research Grants: Regular Program: Competing	Research Grants: Special: Other	Training Programs: Grants	Training Programs: Fellowships	Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
1. Heart and vascular diseases.....	$77,900	$34,667	$3,170	$9,541	$5,075		$57,424		$187,777
2. Lung diseases.....	18,900	10,544	2,270	2,689	1,410		8,802		44,615
3. Blood diseases and resources.....	24,961	7,757	560	870	1,530		14,302		49,980
4. Intramural laboratory and clinical research						$24,383			24,383
5. Research management and program services.								$17,129	17,129
Total Obligations....	121,761	52,968	6,000	13,100	8,013	24,383	80,528	17,129	323,884

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Program	Research Grants: Regular Program: Non-competing	Research Grants: Regular Program: Competing	Research Grants: Special: Other	Training Programs: Grants	Training Programs: Fellowships	Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
1. Heart and vascular diseases.....	$77,125	$23,400	$2,000	$7,377	$6,300		$50,376		$166,578
2. Lung diseases.....	19,400	6,371	2,514	2,635	2,800		5,869		39,589
3. Blood diseases and resources.....	28,475	6,100	350	527	1,315		7,583		44,350
4. Intramural laboratory and clinical research						$24,699			24,699
5. Research management and program services.								$17,578	17,578
Total Obligations....	125,000	35,871	4,864	10,539	10,415	24,699	63,828	17,578	292,794

National Heart and Lung Institute

Budget Mechanism

(Dollars in thousands)

	1975 Estimate			1976 Estimate		
	Number	FTE[1]	Amount	Number	FTE[1]	Amount
Grants						
Regular						
Non-competing...	998		$121,761	900		$125,000
Competing.....	192		19,200	160		24,071
New.....	203		30,500	65		9,000
Supplemental....	(210)		3,268	(100)		2,800
Subtotal.....	1,393		174,729	1,125		160,871
Special						
Research career program.....	171		5,100	133		4,064
Heart cooperative drug study.....	1		900	1		800
Subtotal.....	172		6,000	134		4,864
Total Grants.....	1,565		180,729	1,259		165,735
Fellowships						
Non-competing...	185	185	2,685	478	478	7,415
Competing.....	---	---	---	---	---	---
New.....	280	310	5,330	76	190	3,000
Supplemental....	---	---	---	---	---	---
Subtotal.....	465	495	8,015	554	668	10,415
Training Grants						
Non-competing...	139	556	13,100	125	500	10,539
Competing.....	---	---	---	---	---	---
New.....	---	---	---	---	---	---
Supplemental....	---	---	---	---	---	---
Subtotal.....	139	556	13,100	125	500	10,539
Laboratory & Clinical Research.....	---	---	24,383	---	---	24,699
Research & Development Contracts....	---	---	80,528	---	---	63,828
Biometry, Epidemiology & Field Studies	---	---	---	---	---	---
Research Management & Program Services..	---	---	17,129	---	---	17,578
Total.....			323,884			292,794

[1] Full time equivalents

Heart and Vascular Diseases

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$187,777,000	---	$166,578,000	---	-$21,199,000
Total	---	187,777,000	---	166,578,000	---	-21,199,000
Subactivities:						
Arteriosclerosis	---	49,271,000	---	43,477,000	---	-5,794,000
Hypertension	---	34,357,000	---	30,317,000	---	-4,040,000
Cerebrovascular disease	---	3,964,000	---	3,498,000	---	-446,000
Coronary heart disease	---	37,944,000	---	33,482,000	---	-4,462,000
Peripheral vascular disease	---	4,153,000	---	3,665,000	---	- -488,000
Arrhythmias	---	14,536,000	---	12,827,000	---	-1,709,000
Heart failure and shock	---	17,368,000	---	15,325,000	---	-2,043,000
Congenital and rheumatic heart disease	---	8,873,000	---	7,829,000	---	-1,044,000
Cardiomyopathy and infections of heart	---	3,020,000	---	2,665,000	---	-355,000
Circulatory assistance	---	15,291,000	---	13,493,000	---	-1,798,000
Total	---	187,777,000	---	166,578,000	---	-21,199,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	---	77,900,000	---	77,125,000	---	-775,000
Competing	---	34,667,000	---	23,400,000	---	-11,267,000
Special	---	3,170,000	---	2,000,000	---	-1,170,000
Subtotal	---	115,737,000	---	102,525,000	---	-13,212,000
Fellowships	---	5,075,000	---	6,300,000	---	+1,225,000
Training grants	---	9,541,000	---	7,377,000	---	-2,164,000
Research Development Contracts	---	57,424,000	---	50,376,000	---	-7,048,000
Total	---	187,777,000	---	166,578,000	---	-21,199,000

Based on a National Heart and Lung Institute budget of $292,794,000 it is anticipated that the Heart and Vascular Diseases budget will be approximately $166,578,000 for grants and contracts. This budget would result in a decrease of $21,199,000 from the 1975 estimate. At this level, grant and contract programs in this activity would be reduced by not funding lower priority noncompeting projects.

Cardiovascular disease continues to be the primary health problem in the United States. It is estimated that 28,000,000 Americans are afflicted with some form of heart or blood vessel disease: 23,000,000 of them have hypertension, 3,900,000 suffer from coronary heart disease and 1,700,000 from rheumatic heart disease, while 1,650,000 have had one or more strokes. In 1972, an estimated 1,060,000 Americans died from heart and blood vessel diseases; this represented more than 54 percent of deaths from all causes.

In response to the enabling legislation, the National Heart and Lung Institute continues to develop and support an integrated program embracing fundamental and clinical research, manpower development and training to satisfy projected needs. It supports prevention, control, and education activities to provide for efficient and timely application of knowledge obtained through research. The Institute employs all appropriate available support mechanisms such as investigator-initiated research projects, program project grants, Specialized Centers of Research (SCORS), a National Research and Demonstration Center, targeted research and development contracts, and intramural research to develop and support its cardiovascular programs.

Major Problem Areas

For more than fifty years, heart and blood vessel diseases have been the major cause of death in this country. They now account for 54 percent of all deaths annually. This is more than three times the death rate from cancer, the next highest cause. An estimated 28 million Americans have diseases of the heart and blood vessels, resulting in a large burden of acute and chronic illness and disability. Hence, there is reason for referring to heart and blood vessel diseases as the modern epidemic. Moreover, heart and blood vessel diseases cost the economy more than $30 billion per year in lost productivity and expenses for medical care.

Ten major problem areas in heart and blood vessel diseases are defined below. Of these, arteriosclerosis and hypertension are considered the major fundamental cardiovascular disease problems in the United States; some of their major manifestations are coronary heart disease, cerebrovascular disease, arrhythmias, heart failure and shock. The causes of arteriosclerosis and most cases of hypertension are unknown.

Arteriosclerosis

Arteriosclerosis or "hardening of the arteries" is the condition that may commonly underlie heart attack, heart failure, stroke, and other illness of the cardiovascular system. It is the chief cause of death in the United States and is by far the most common of the serious diseases affecting man in Western society. It is the basis for more than four-fifths of the deaths from diseases of the heart and blood vessels in this country and thus forms the basis of almost half of the deaths from all causes.

It represents a chronic progressive pathologic change in which the inner lining of the arteries becomes rough, thick, hard and covered with lipid-rich plaques. Eventually the inner diameter of the vessels decreases and blood flow in the diseased arteries diminishes or stops completely. Arteriosclerosis begins early in life and generally becomes manifest in middle age or later. Until it does become manifest as heart attack, stroke, or other illnesses, it is often without symptoms and is therefore undetected. Its clinical manifestations may be as abrupt as catastrophic illness.

Virtually all adult American males, and post-menopausal women, are afflicted to some degree. The economic impact of arteriosclerotic disease in the United States has been estimated at $26 billion per year in wages, lost productivity, and expenses for medical care. If arteriosclerosis could be prevented, hundreds of thousands of lives might be prolonged. International statistics reveal a great variation in death rates for atherosclerotic coronary heart disease. For instance, in Denmark and Sweden the death rate for men under the age of 55 is less than half that for the same age group in the United States; in many countries it is far lower and in some, for example Japan, it is a rare condition. This difference indicates that the high death rates due to arteriosclerosis in the United States are neither

necessary nor inevitable. Although attempts to learn why the United States fares so poorly in these comparisons have not been conclusive, studies have suggested that differences in diet, life-style and personal habits may be important. Risk factors associated with an increased rate of development and progression of arteriosclerosis are age, sex, high levels of cholesterol in the blood, high blood pressure and smoking. Of these, the latter three can potentially be controlled, and considerable effort is currently being expended in the National Program to learn more about these as well as other factors which may play a role in the development of atherosclerosis.

Hypertension

Hypertension or high blood pressure, is a common and often serious condition. An estimated 23 million adult Americans or about 15 percent of the adult population have some degree of hypertension. It is more common in the black poulation than in the white population. It is a risk factor for heart attack and heart failure and it is the major predisposing factor for stroke.

Hypertension can be treated and treatment reduces the incidence of stroke and heart failure. It is uncertain at present whether treatment will also reduce the incidence of heart attacks. It is also uncertain whether slight or mild degrees of hypertension require treatment. Current treatment, while effective, is unsatisfactory in that it requires lifelong adherence to medication, is expensive, has some side effects and must be individualized. In nine out of ten cases of hypertension the cause of the disorder is unknown and hence we lack the means to prevent or cure it even though treatment and control are possible.

High blood pressure is easily detected, but may exist for many years without symptoms. While it can be controlled with available therapy, of the millions of Americans with this disease, one-half are probably unaware that they have it, and of those who are aware, less than one-half are receiving adequate therapy. The National Program is expending efforts both on research to discover the causes of hypertension and on programs to educate the public about the dangers of hypertension and the benefits of treatment.

Cerebrovascular Disease

Cerbrovascular disease occurs when an artery supplying blood to the brain is blocked, ruptured, or injured. Cerebrovascular disease is due primarily to arteriosclerosis, and hypertension is the basis for the great majority of strokes. The individual and public health burden of death, paralysis, and brain damage from cerebrovascular disease is large. Of the 1.7 million adults who have this disease, 800,000 are partially or completely disabled, and 200,000 reside in nursing homes. Stroke kills about 200,000 persons a year particularly at older ages. The death rate is greater among men than women, and greater among blacks than whites. Each year nearly 600,000 patients are discharged from our hospitals with a diagnosis of stroke, and each year about 250,000 individuals, between the ages of 25 and 64, are crippled mentally or physically by a stroke. Many more lives could be saved and disabilities prevented if we had effective methods for prevention and treatment of arteriosclerosis and hypertension, and if available treatment were more widely applied. It should be noted that due to the recent advances in therapy for high blood pressure, there has been an appreciable long-term decrease in deaths from stroke.

While the National Institute of Neurological Diseases and Stroke is primarily responsible for programs on those aspects of stroke that deal with brain injury and its consequences, the NHLI is responsible for programs on the cerebrovascular pathology that underlies the stroke.

Coronary Heart Disease

Coronary heart disease refers to the consequences of atherosclerosis in the arteries that supply the heart muscle. A heart attack is a manifestation of coronary heart disease and occurs when a coronary artery is blocked, preventing the blood from reaching the heart muscle normally nourished by the artery. This produces death of the heart muscle, technically called myocardial infarction. Depending upon the site of the coronary blockage, a small or a large fraction of the total heart may be involved.

Heart disease associated with arteriosclerosis of the coronary arteries remains the predominant form of heart disease in the adult American population. It is responsible for chronic illness in 4 million Americans, 2.5 million below the age of 65. In 1972, coronary heart disease accounted for about 685,000 deaths in this country, It is the largest single cause of death from cardiovascular disease and is the leading cause of death in men after age 38 and in women after age 55. Each year, approximately 170,000 persons below age 65 die of coronary heart disease.

Coronary heart disease may also result in angina pectoris (a transient pain usually located in the center of the chest and left arm that is brought on by exercise, exposure to cold, and other factors), heart failure (impaired pumping performance of the heart leading to accumulation of fluid in the body and congestion in the lungs), disturbances of heart rhythm and sudden death. Each year about 400,000 deaths from coronary heart disease occur before hospitalization. Half of these occur instantaneously and unwitnessed. Over three-quarters of these victims have known coronary artery disease or high blood pressure before their sudden deaths, but in the rest, sudden cardiac death is the first evidence of heart disease.

Coronary artery bypass surgery has been perfected surgically and can bring increased blood supply to endangered heart muscle. This technique uses a blood vessel graft to bypass narrowed or occluded segments of coronary arteries. Over 25,000 such operations are being done annually in the United States, with hospitalization costs in excess of $5,000 for each operation. Although such surgery generally provides substantial decrease of symptoms in patients with severe angina pectoris, the long-term effects upon mortality and the clinical circumstances in which it is preferable to medical therapy are not adequately defined. The answers to these questions are the focus of clinical trials being established in the National Program.

Following heart attack or other manifestation of heart disease, tens of thousands of Americans annually are left with substantial impairment of their ability and freedom to function and to contribute to society. Thus, one aspect of the National Program in Coronary Heart Disease deals with the development of improved methods of rehabilitation. The survivors of heart attacks are particularly prone to a recurrence. Measures that prevent such recurrence may also be useful in the primary prevention of the first heart attack.

Improved understanding of the onset, causes of heart malfunction, mode of death and corrective procedures would have a marked effect on the exceedingly high morbidity and mortality of coronary heart disease, and the National Program is exerting major effects to solve these problems.

Peripheral Vascular Diseases

Peripheral vascular diseases are the cause of considerable suffering and disability. They are abnormalities that occur within arteries or veins. Atherosclerotic narrowing may result in inadequate blood flow through the arteries. The veins may become dilated (varicosities) or inflamed and obstructed by blood clots (thrombophlebitis). These diseases may be painful and result in organ damage, skin

ulcerations and gangrene. Peripheral vascular disease in the legs may affect the ability to walk or run. Thrombosis in the veins may produced pulmonary embolism; i.e., clot fragments may be carried in the blood from their site of origin to the lungs. This in turn may result in shock and death. About 265,000 patients are discharged from hospitals each year with a primary diagnosis of peripheral vascular disease.

Surgeons have developed techniques to replace or bypass diseased arteries with vascular or prosthetic grafts. Otherwise, peripheral arterial disease, peripheral venous disease and disorders of the lymphatics have been the focus of only a limited research effort in the past. The National Program is placing increased emphasis on research in this area.

Arrhythmias

Arrhythmias, or abnormal heart rhythms, are one of the most common manifestations of various types of heart disease and they are frequently the immediate cause of heart failure and death. Arrhythmias result from an alteration in the normal generation and transmission of electrical impulses within the heart. They may also occur without recognizable disease. Many rhythm disturbances have minor influence upon life expectancy and cause little disability, while others cause serious symptoms, and some are almost instaneously fatal. For example, arrhythmias kill more than half of the patients with coronary heart disease and are a major problem in patients with rheumatic heart disease.

Important new concepts are developing in the National Program concerning the basic mechanisms of arrhythmias and the correlation of electrical signals from the heart to the extent, severity, and prognosis of heart disease. Information is being accumulated about the different causations of arrhythmias and their differential responses to drug and surgical therapy. Identification of arrhythmias that carry a high risk of sudden cardiac death is fundamental to the development of preventive measures. The analysis of spontaneous rhythms and the influence of drugs must be assessed by quantitative analysis of extensive electrocardiographic tape recordings. Substantial progress has been made toward performing this task automatically, rapidly, and quantitatively by computer.

The National Program is concerned with the development of improved methods for prevention, diagnosis, and management of arrhythmias.

Heart Failure and Shock

Heart failure and shock represent major causes of death and may be the consequence of various disorders ranging from inadequate pumping by a severely damaged heart (cardiogenic shock), loss of blood (hemorrhagic shock), and impairment in the control of arterial tone. Heart failure occurs when the heart has been damaged so extensively that its ability to pump blood is impaired and it can no longer meet the needs of the body. In its chronic form, it is often associated with shortness of breath, accumulation of fluids and swelling of the legs. Shock is also a secondary phenomenon characterized by an inability of the heart and peripheral arterial tone to maintain adequate blood pressure and blood perfusion. Left untreated, it rapidly leads to irreversible damage to such critical organs as the kidney and brain, and ultimately, to death.

Heart failure and shock are the most common causes of in-hospital deaths from heart attack and most other types of heart disease, thus accounting for about a quarter of a million deaths annually. In addition, chronic heart failure may follow a heart attack or result from high blood pressure or other cardiovascular diseases. About two million Americans have chronic heart failure. In the majority of chronic heart failure patients, symptoms can be relieved by drugs.

In the absence of valvular lesions or intracardiac defects, insufficient surviving or poorly functioning heart muscle is the immediate cause of heart failure and shock in most instances. An improved understanding of energy utilization in heart muscle is essential for adequate control or prevention of heart failure and shock in these cases.

The amount of irreversibly damaged heart muscle is not predetermined at the onset of a heart attack; there is a zone which is in jeopardy but has not yet progressed to irreversible damage. Current research within the National Program has identified several promising means for protecting this zone of potentially reversible damage and for promoting its recovery. Methods to quantify the amount of heart muscle which is inadequately perfused or which has undergone irreversible damage are crucial to the evaluation of various modes of therapy. Other aspects of the diagnosis, etiology, therapy, and prevention of heart failure and shock are also receiving emphasis in the National Program. These include research on improving the pumping function of the heart, understanding and treating the disturbances of the regulation of peripheral blood vessels, and the evaluation of altered hormonal and kidney functions.

Congenital and Rheumatic Heart Diseases

Congenital and rheumatic heart diseases are important disorders of childhood, and may form the basis for considerable impairment of the quality of life of the patients surviving into adulthood. At present there are 35 recognizable types of congenital or inborn heart defects and about 25,000 babies are born each year with heart defects. The post-natal mortality from heart defects is about 7,500 per year. In addition, there are 100,000 children and 1,600,000 adults with known rheumatic heart disease with an annual mortality of about 15,000.

Congenital heart disease occurs when the heart or major blood vessels near the heart fail to mature normally before birth. About half of the children born with this disease do not survive until their first birthday. The causes of congenital heart disease are generally unknown. Less than 3 percent are known to be related to a particular event or disorder occurring during pregnancy, such as rubella, (german measles) infection, or the use of certain drugs, such as thalidomide.

The earliest surgical success in the treatment of heart diseases were in the correction, or palliation, of congenital heart disease. These successes are being exploited in the development of diagnostic and surgical techniques applicable to the newborn. Important insights have also been gained into the development of the cardiovascular system. Still, in most cases, science does not know what makes the heart develop abnormally before a baby is born.

Rheumatic fever and rheumatic heart disease were once considered leading causes of serious childhood illnesses. They can now be prevented. Rhematic fever is almost always preceded by a stretococcal infection and can be prevented by prompt treatment of such infections. Rheumatic heart disease is an immunological disturbance that frequently occurs years after initial rheumatic fever and prior streptococcal infection. This type of heart disease may lead to serious damage of the heart valves. This, in turn, may not only shorten life, but also seriously impair the quality of the patient's life. Improved understanding and control of immunological problems is thus important in the identification of susceptibility and the prevention of rheumatic heart disease, as well as in the success of cardiac transplants and in the prevention of cardiomyopathy and possibly other forms of heart disease.

Each year rheumatic fever afflicts about 100,000 school children. Both congenital and rhematic heart diseases cause substantial impairment to the health of children and adults in their most productive years. Respectively, in the United States, they annually cause about 7,500 and 15,000 deaths.

The National Program is placing increased emphasis on efforts to understand better the causes of congenital heart disease, and on studies of the immunological problems associated with heart disease.

Cardiomyopathies and Infections of the Heart

Cardiomyopathies and infections of the heart are diseases of the heart muscle and its lining. These diseases cause enlargement of the heart, heart failure, irregularities of the heart rhythm, and occasionally sudden death. The prevalence of these diseases, caused by a variety of factors, is unknown. Known factors producing cardiomyopathies include toxic substances, viral infections, alcohol, immunologic phenomena, nutritional deficiencies, muscular dystrophy, and a number of rare diseases. The condition may be acute or chronic and progressive. Rapidly fatal disease may be associated with heart failure, disturbances of rhythm and sudden death. Infections may affect the heart muscle (myocarditis), its interior wall (endocarditis), or its exterior surface (pericarditis). They may be caused by certain viruses, bacteria or fungi. Cardiomyopathies and myocarditis are being recognized with increasing frequency. However, because we still lack specific diagnostic criteria and laboratory tests, quantitative information concerning the prevalence of these diseases is not available.

The National Program is placing increased emphasis on improved understanding of the causes of cardiomyopathies.

Circulatory Assistance

Present and forseeable techniques of general pharmacological management of acute and chronic cardiac insufficiency and shock still leave a substantial fraction of patients with compromised or fatally impaired heart function. By mechanical supportive means, it is possible to substitute some of the pumping function of the heart and to relieve its workload. Presently, such techniques are possible briefly in man and for longer periods in the experimental animal.

Circulatory assistance to the failing heart may be provided by many types of devices currently under development. Some are applied externally to the lower extremities in synchrony with the heart beat. In others, the pumping action of the heart is enhanced by synchronously expanding an collapsing a "balloon" positioned in the aorta, the artery leading from the heart. On a very limited scale, a few devices have been employed which require substantial surgery and the actual positioning of a pumping device within the chest. While circulatory assist devices are designed to improve the mechanical function of the heart, the apparatus also generally involves important electronic, pneumatic, hydraulic, and mechanical systems.

Highlights of Recent Progress and Accomplishments

Arteriosclerosis--Improved Diagnosis. An intensive program has been launched to develop and assess new and improved instrumentation and techniques for noninvasive detection, characterization, and quantification of atherosclerosis. This instrumentation is urgently needed for research to assess treatments that may retard or reverse arteriosclerosis. The instrumentation will also be of use in the diagnostic study of perons with symptoms and in identifying dangerous arteriosclerotic narrowing in patients without symptoms.

Heart Disease--Improved Diagnosis. A new diagnostic technique called echocardiography, which uses reflected ultrasound to provide a cross-sectional image of the heart in three dimensions, is proving uniquely valuable in the diagnosis of a variety of congenital and acquired heart disorders. The technique is painless, noninvasive, and safe as well as highly effective. It frequently provides information on

structural abnormalities and their effects on heart performance that cannot be readily obtained by conventional X-ray techniques, such as angiography. In many instances, echocardiography may obviate the need for angiography, a procedure that may carry some hazard in critically ill patients.

Heart Attacks--Improved Detection of Risk Factors. Over the last two years the Lipid Research Clinics Program has evaluated available technology and developed with industry rapid, inexpensive, accurate, and precise methods for determining the level of certain blood lipids (cholesterol and triglyceride). This demonstrates that accurate and precise values for blood lipids can be obtained by a group of high volume laboratories. This standardization is finding wide application in many clinical chemistry laboratories in this country, thereby improving the accurate detection of one of the three major coronary heart disease risk factors. Standardization also assures the comparability essential for the success of large-scale Lipid Research Clinic Prevalence and Prevention Studies.

Heart Disease--Improved Dietary Data Collection. A key element in a number of studies of the relationship of diet to heart disease is the collection and analysis of information on the eating habits of persons being studies. In 1974 the dietary data collection procedures for the Multiple Risk Factor Intervention Trial (MRFIT) study were finalized. The Lipid Research Clinic Programs are collaborating in this project so that identical dietary data collection procedures can be carried out in the two large-scale studies to insure comparability. This has involved a number of activities. A new open-ended food composition table, based on standard references, has been developed in a format designed to meet study needs. Figures for fatty acids, carbohydrates, and dietary cholesterol have been verified or updated, with the help of the U.S. Department of Agriculture. Coding methods have been developed which allow for a maximum of automation. A Central Nutrition Coding Center is being established at the MRFIT Coordinating Center which will process the dietary records of both studies. A system has been developed for computerized calculation of recipes.

Premature Heart Disease--Prevention. In July, 1973, after two years of extensive preparation and planning, the continent-wide network of Lipid Research Clinics and their support facilities began a study to determine whether reducing blood cholesterol levels in patients with Type II hyperlipoproteinemia can slow down or prevent the development of premature coronary artery disease. Recruitment of subjects for this seven-year trial was initiated during the second half of 1973. Healthy men, 35-59 years old with elevated cholesterol are eligible. In 1974 almost 4,500 men participated in the first prerandomization visit and many more thousands were screened. Over 750 have been randomized into drug or placebo groups. Completion of recruitment is projected for January, 1976. Initially, physician and laboratory referral of prospective subjects was emphasized; more recently, newer recruitment strategies, including industrial and blood bank screening, media support, and other more creative case-finding techniques are being used.

Heart Attacks--Efforts to Decrease. The purpose of the Multiple Risk Factor Intervention Trial (MRFIT) is to determine whether or not a preventive program directed at a reduction of elevated blood lipids (cholesterol), reduction of high blood pressure, and reduction or elimination of cigarette smoking will result in a significant reduction in deaths from coronary heart disease. Over 150,000 men aged 35-57, have been screened for coronary heart disease risk factors to determine their eligibility for participation in the MRFIT. From this group more than 13,000 have been found to have increased risk of developing coronary heart disease and have expressed willingness to participate in this six-year research effort. Of these, 5,196 have met all criteria for eligibility and have been enrolled in this primary prevention clinical trial. The recruitment effort is being conducted by 20 clinical centers in 14 areas of the country, and the enrollment goal of 12,000

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men with higher than average risk of developing heart disease is expected to be reached during calendar 1975.

Heart Attacks--Treatment. Nitroglycerin, one of oldest and best drugs for relieving the chest pain of angina pectoris, may also be uniquely valuable in the treatment of acute heart attacks. Recent animal experiments have shown that nitroglycerin reduced the extent and severity of heart muscle damage resulting from blood deprivation, which is often a critical factor affecting survival, and also the amount of residual disability after recovery from heart attacks. The drug also helped protect the heart against rhythm disturbances, a common and sometimes lethal complication. The drug is currently undergoing clinical evaluation in heart attack patients.

Heart Attacks--Reducing the Damage to Heart Muscle. Recent experimental studies have shown that when the blood supply to heart muscle is cut off by a heart attack the amount of heart muscle irreversibly damaged can be reduced by several different techniques. Reducing the workload of the heart by the very careful administration of drugs to slightly reduce the blood pressure, or by mechanical devices (the "intra-aortic balloon") have shown very encouraging results in limited clinical studies. Several promising drugs increase blood flow to the heart muscle, some by reducing swelling, others by dilating vessels, and yet others apparently by increasing diffusion of nutrients in the tissue. The provision of glucose in high concentrations in the presence of potassium and insulin provides higher concentration of nutrients and seems to offer benefit as well. On the basis of these promising laboratory and clinical studies, an expanded program for protecting jeopardized heart muscle has been launched.

Heart Disease--Efforts to Decrease Mortality. Thirty Clinical Centers, a Coordinating Center, and an ECG Reading Center have been selected for the Aspirin-Myocardial Infarction Study. This is a randomized, placebo-controlled, double blind study of the efficacy of 1 gram of aspirin per day in preventing mortality in men and women with documented coronary heart disease. Recruitment will start in May of this year of 4,000 patients aged 30-69 and is scheduled to be completed within the year. The patients will be observed for three years while on study medication.

Heart Surgery--Coronary Artery Bypass. The surgical placement of a bypass graft around a narrowed or occluded coronary artery has been extensively developed and widely practiced with over 25,000 operations in the past year alone. In a substantial majority of patients with severe angina pectoris (pain from heart disease), the procedure results in relief of symptoms. However, the long-term effects as to the length of life and the specific indications in other patients remain ill defined. Accordingly, a collaborative trial to assess these factors is going through the pilot phase stages preparatory to full-scale implementation.

Recurrent Heart Attacks--Evaluation of Therapy. Do drugs that reduce levels of certain blood lipids (cholesterol and triglyceride) confer any protection against recurrent heart attacks or improve long-term survival among men who have previously experienced one or more acute heart attacks? Apparently not, according to findings from the just completed Coronary Drug Project (CDP). This study is a nationwide collaborative trial. The primary objective was to evaluate the efficacy of five lipid-lowering drug regimens in the long-term treatment of coronary heart disease in men aged 30-64 with ECG evidence of previous heart attack. There were 53 clinics participating in the CDP along with a Coordinating Center, Central Laboratory, ECG Reading Center, Drug Procurement and Distribution Center, and an Institute Medical Liaision Office. A total of 8,341 patients were enrolled. All patients were randomly assigned to one of the six treatment groups in a double blind fashion and were followed for a minimum of five years. It should be noted that the drugs themselves failed only in the limited sense that their lipid-lowering effects did not benefit the patients who had already sustained heart attacks. The results may

be quite different when they are used to reduce the threat of first heart attacks by intervening specifically against elevated blood lipids in asymptomatic patients.

Heart Disease--Rehabilitation. A task force has reported upon the needs and opportunities for improved rehabilitation of patients with cardiac disease, particularly coronary heart disease. The report addresses itself to medical, psychological, and sociological factors needed to maximize the return of the patient with coronary heart disease to his maximum potential.

Heart Disease--Specialized Centers of Research. For a number of years the Institute has supported an extramural research program directed specifically at the improved understanding, prevention, and treatment of heart attack or myocardial infarction. The single largest part of this program has been the Myocardial Infarction Research Units which combine broad programs of clinical research with fundamental laboratory studies and developments in relevant technology and investigative methods. Much of the improvement in the understanding and treatment of heart attack over the past five years has come from these units which will have completed their program in 1975. As an outgrowth of that program, to build upon it and broaden the topics of research, the Institute implemented a program of Specialized Centers of Research on Ischemic Heart Disease. The objective of this program is multidisciplinary clinical and fundamental research directed at the reduction of death and disability from all forms of ischemic heart disease, including not only myocardial infarction, but also chronic forms of the disease including angina pectoris, rhythm disturbances and heart failure. The research program is also directed to techniques of rehabilitation and problems of sudden cardiac death.

Heart and Blood Vessel Diseases--Animal Models. Progress in understanding the causes and in developing treatment for heart and blood vessel diseases has benefited greatly from research in animals. The closer the animal models are to man the more likely it is that the results of studies will be helpful in studying the condition in man. Non-human primates offer a very good opportunity to conduct studies and observations that will contribute to further progress in this area. The Institute has embarked on a program to make non-human primate models of certain cardiovascular disorders available on a broad scale to investigators. This program, announced late last year, will cover breeding, supply, and study of several varieties of monkeys and baboons. Some of the animals will be given diets or other treatments to induce chronic atherosclerosis or hypertension. A search will also be made for animals with spontaneous disorders of lipid metabolism or blood pressure, and these will be studied both genetically and metabolically.

High Blood Pressure--National Education Program. In 1974 the National High Blood Pressure Education Program reached the stage of becoming fully operational. Nearly 100 national organizations cooperated in the planning and implementation of the first National High Blood Pressure Month in May 1974. Among the activities conducted as a result of the month was the screening of over 400,000 persons and referral of 76,000 of them with elevated pressures to a physician or clinic for further evaluation. Close to 10,000 articles on hypertension appeared in newspapers at the time of the High Blood Pressure Month, and articles on hypertension were published in magazines and professional journals having a combined circulation of close to 4.5 million. During 1974 the Program secured free broadcast time equivalent to $4 million on television and over $200,000 on radio. In 1974 the High Blood Pressure Information Center answered more than 28,000 requests for information and published materials, and handled responses to over one-half million requests as a result of three newspaper columns by Ann Landers. The American Dental Association House of Delegates passed a resolution in November 1974 endorsing the National High Blood Pressure Education Program and strongly encouraging continuing education in hypertension for dentists. The Program was similary endorsed in December 1974 by the Office of Professional Standards Review Advisory Council which recommended to local PSROs a high priority for hypertension and use of program developed guidelines.

High Blood Pressure--Education Research Program. Research was initiated last spring on new methods of educating the public and professionals about hypertension. Among the topics covered are: hypertension education for a low income community, improving patient compliance through nursing action, assuring patient compliance by health care contracts, and health education strategies for hypertension control. Results of these efforts will be utilized in further development of the patient education component of the National High Blood Pressure Education Program.

High Blood Pressure--Benefits of Treatment. The Hypertension Detection and Follow-Up Program (HDFP) completed home screening for high blood pressure of over 160,000 persons to identify and enroll its goal of at least 10,500 persons with diastolic blood pressure of 95 mm Hg or higher into a five-year study to determine the benefits of high blood pressure control in the general population. The purpose of the program is to assess the ability of a program of long-term antihypertensive therapy to reduce mortality and morbidity from high blood pressure in persons aged 30-69. It is expected that the results of this study will show the potential for saving lives in the large number of persons known to be afflicted with this disorder. The prevalence of high blood pressure found for black males of this age was 27 percent, black females 22 percent, non-black males 13 percent, and non-black females 8 percent. Early data from one year of follow-up of the 11,500 randomized participants reveal that, of those under continuing direct care of the HDFP clinics, 72 percent have had their blood pressure reduced to their goal levels. Blood pressure levels have also been reduced for the group receiving regular care by physicians in the community at large.

High Blood Pressure--Periodic Variations. Blood pressure, blood electrolytes, and the output of hormones and other biologically active substances believed to be involved in the regulation of blood pressure are subject to periodic variations lasting approximately 24 hours (circadian rhythms). The recent development of fast, accurate, and sensitivie techniques for measuring these substances or the products of their metabolism in blood, urine, and other body fluids in making possible more precise evaluation of these rhythms, their effects on blood pressure, and also on the results obtained with various therapies for hypertension. A fuller understanding of these rhythms promises to help in maximizing the effectiveness of drug therapy while reducing the incidence and severity of undesirable side effects.

High Blood Pressure--Behavioral Aspects. Many persons with high blood pressure are either unaware of their condition or are reluctant to embark on and adhere to treatment available for controlling it. One of the most important challenges, therefore, of the National High Blood Pressure Education Program is to devise approaches to modify the psychological and social factors that influence a person's adherence to a therapeutic regimen. In order to increase its understanding of this problem, this program is embarking on a study of the characteristics of an individual that relate to adherence behavior and the educational interventions that will enhance a patient's initial and long-term adherence to therapy.

High Blood Pressure--Possible Side Effects of Therapy. The Institute is cooperating with the Food and Drug Administration (FDA) in evaluating a reported association between the use of reserpiue and the occurrence of breast cancer. Reserpine is one of the oldest effective medicines to reduce high blood pressure, has been used for over 20 years, and has been a mainstay of antihypertensive therapy in many thousands of individuals. Preliminary examination of the data found in three retrospective case-control studies has led the Institute and its advisors to the conclusion that significant problems or deficiencies exist in the nature of such hospital case control data which do not allow conclusive judgement of the results of these studies. The FDA is convening an expert panel to review the data and, if necessary, to recommend research or data collection efforts to resolve the issue. In the meantime, the Institute and its technical advisors have recommended that the use of reserpine be continued according to protocol in the Hypertension Detection and Follow-Up

Program and that women on the study be alerted to the reported findings and offered the choice of being removed from reserpine therapy.

High Blood Pressure--Possible Side Effects of Therapy. Spironolactone (a steroid) a drug in clinical use as a diuretic and antihypertensive agent, may produce in some males such side effects as breast enlargement, reduced sexual drive, and impotence. Studies in several species of animals have shown that the drug reduces the ability of the gonads to synthesize the male sex hormone, testosterone. Studies are now underway among human volunteers to assess the effects of spironolactone on plasma levels of testosterone and other hormones that may be involved in various side effects of the drug.

High Blood Pressure--Animal Models. A strain of rat has been bred that is genetically hypertensive, and a subgroup of that strain is especially prone to stroke as a result of hypertension. Efforts are underway to develop a monograph to assess the appropriateness of the genetically hypertensive rat as the best animal model of human essential hypertension, and to establish breeding, care, and maintenance guidelines for these animals and their appropriate control rates with normal blood pressure. The Institute has coordinated the establishment of a resource colony of stroke-prone rats by the National Institutes of Health's Division of Research Services to provide standardized breeding stock for scientists throughout the world.

High Blood Pressure--Specialized Centers of Research. In June 1974, a Program Announcement and Guidelines for Hypertension Specialized Centers of Research (SCOR's) was issued. Applications in response to this announcement will be reviewed in 1975 and awards made in FY 1976. This continuation of the Hypertension SCOR's reflects the contribution the current SCOR's are making in a coordinated and focussed research program, and indicates the favorable assessment by the Institute and its scientific advisors of the value of this program.

Heart Assist Devices. Progress continues to be made in developing materials, components, and systems for circulatory assist and cardiac replacement or artificial heart devices. No totally satisfactory synthetic material has been developed for long-term use in implanted devices, but a number of leads are being followed, and continued progress is being made in improving the compatibility of several types of materials and surfaces with blood. The energy systems to power implanted devices are under investigation, and improvements in efficiency, performance, and endurance have been achieved. One indication of progress in this area is an experiment in which the heart of a calf was replaced by an artificial heart which operated satisfactorily for over three months.

Lung Diseases

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$44,615,000	---	$39,589,000	---	-$5,026,000
Total	---	44,615,000	---	39,589,000	---	-5,026,000
Subactivities:						
Structure and function of the lung	---	12,051,845	---	10,694,172	---	-1,357,673
Pediatric pulmonary disease	---	3,708,260	---	3,290,514	---	- 417,746
Emphysema and chronic bronchitis	---	8,923,000	---	7,917,800	---	-1,005,200
Fibrotic and immunologic lung disease	---	5,678,272	---	5,038,600	---	- 639,672
Respiratory Failure	---	10,197,715	---	9,048,914	---	-1,148,801
Pulmonary vascular disease	---	4,055,908	---	3,599,000	---	- 456,908
Total	---	44,615,000	---	39,589,000	---	-5,026,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	---	$18,900,000	---	$19,400,000	---	+ $500,000
Competing	---	10,544,000	---	6,371,000	---	-4,173,000
Special	---	2,270,000	---	2,514,000	---	+ 244,000
Subtotal	---	31,714,000	---	28,285.000	---	-3,429,000
Fellowships	---	1,410,000	---	2,800,000	---	+1,390,000
Training grants	---	2,869,000	---	2,635,000	---	- 54,000
Research & Development Contracts	---	8,802,000	---	5,869,000	---	-2,933,000
Total	---	44,615,000	---	39,589,000	---	-5,026,000

The 1976 estimate for Lung Diseases results in a decrease of $5,026,000 from 1975. At this level grant and contract programs in this activity would be reduced by not funding low priority noncompeting grants.

Diseases of the lung constitute a major national health problem of increasing dimensions. In the United States, lung diseases covered by the program account for an estimated 150,000 deaths each year, cause 45 million days lost from work, 40 million days of bed-restricted activity, and cost the economy approximately $6 billion a year in lost productivity and wages and medical care costs.

In September 1972, the National Heart and Lung Institute appointed the Lung Diseases Panel to develop and recommend a program responsive to the legislative requirements of the National Heart, Blood Vessel, Lung, and Blood Act of 1972. The recommendations of the Lung Diseases Panel were reviewed by the Institute, the National Heart and Lung Advisory Council, and the Interagency Technical Committee, and formed the basis for developing the Institute's expanded program on lung diseases, as well as for developing the plans for coordination of the overall National Program in lung diseases. The lung program, as initially formulated by the Lung Panel, has been reviewed and updated annually by the Institute. The updated National Lung Diseases program reflects the thinking of the Institute staff, the Pulmonary Diseases Advisory Committee, and the lung community of physicians and biomedical scientists to which the Institute looks for professional judgement and advice. It represents an orderly expansion of the Institute's activities relative to pulmonary diseases.

The first Annual Report of the Director of the National Heart and Lung Institute, February 13, 1974, identified some achievements of the lung community toward implementing recommendations of the Lung Diseases Panel. The program continues to be responsive to the Legislative Act, which encourages special attention to childhood diseases, chronic lung diseases, and the establishment of National Research and Demonstration Centers. The Institute's program, which addresses immediate as well as long-range objectives, centers on three specific approaches of comparable importance and urgency:

- Research on the structure and function of the lung in order to gain fundamental information which will improve our understanding of important factors in the promotion of health and the prevention and treatment of lung diseases

- Expansion and development of our knowledge base of specific diseases which constitute national health problems, but which represent areas where current information is insufficient to provide immediate solutions

- Application of available technical resources to solve specific problems, solutions of which are expected to pay immediate dividends in improving the health of our nation.

The disease categories addressed by the National Heart and Lung Institute do not include cancer of the lung, which is the purview of the National Cancer Institute, or acute upper respiratory infections or tuberculosis, which are the responsibility of the National Institute of Allergy and Infectious Diseases.

Major Problem Areas

Respiratory diseases that represent national health problems include chronic obstructive pulmonary diseases (COPD), acute respiratory distress syndromes (RDS), and interstitial lung diseases. The economic cost of these diseases has been estimated at $6.3 billion per year.

Lung diseases afflict both the young and the old. In the newborn, the most common cause of death is the respiratory distress syndrome which affects between 50,000 and 100,000 babies in the United States each year. RDS is implicated in the development of adult respiratory diseases as well. Interstitial lung diseases are a major cause of lung problems in the young adult, and may cause COPD. Of the adult respiratory diseases, emphysema and chronic bronchitis are the major causes of death. An estimated 10 million Americans are currently affected by these diseases, together with asthma. Emphysema and chronic bronchitis represent a particularly pressing health problem since the death rate and prevalence of these conditions have been increasing at an alarming rate over the past 15 years. As a disabling disease, emphysema is the third leading cause of worker retirement on Social Security disability payments. Six major problem areas in the National Program are defined below:

Pediatric Pulmonary Diseases

Pediatric pulmonary diseases present health problems of national dimensions. Hyaline membrane disease (respiratory distress syndrome of the newborn), cystic fibrosis (an inherited disease of abnormal mucus secretion), and bronchiolitis (acute airway obstruction in young children) are among the most important disorders of childhood that involve the lung and the airways. About 40,000 babies are born each year with hyaline membrane disease. Many of these will die unless given prompt treatment, presently unavailable except in a few specialized facilities.

Cystic fibrosis occurs in about one of every 2,000 live births and approximately 5 percent of the general population in the United States carries the gene for this disorder. Cystic fibrosis is one of the main causes of chronic illness in children in the pediatric age group. Bronchiolitis is a common pediatric disorder, but data are not available on its incidence.

Emphysema and Chronic Bronchitis

Emphysema and chronic bronchitis are among the major causes of mortality and illness from pulmonary diseases. Emphysema is a disease in which the thin walls in the alveoli (air sacs) lose their elasticity and tear. Chronic bronchitis refers to a persistent inflammation of the lungs characterized by recurrent coughing and excess mucus in the airways. These diseases may be associated with certain risk factors, such as cigarette smoking, and in some cases with genetic determinants (e.g., deficiency of alpha$_1$-antitrypsin enzyme). Emphysema is a leading cause of death in this country and an even greater cause of disability. Data from 1967 indicate that chronic bronchitis and emphysema account for half of the total 181,000 man-years lost due to lung diseases. The crude death rate for chronic bronchitis doubled between 1950 and 1967. The death rate for emphysema increased thirteen fold in the same period to a level of 10.6 per 100,000 population. Since 1968 the rate decreased 10% for chronic bronchitis and 12% for emphysema.

Fibrotic and Immunologic Lung Diseases

Fibrotic and immunologic lung diseases are induced by many factors. Fibrotic responses (proliferation of connective tissue or scar formation) and immunologic responses are characteristic of a variety of lung diseases. Among the factors that may induce these responses are exposure to substances such as coal dust, silica, and asbestos in the environment; viral and bacterial infections; diseases of the connective tissue such as rheumatoid arthritis, lupis, and scleroderma; radiation damage; and exposure to substances like molds and dust that initiate hypersensitivity reactions. Diseases characterized by pulmonary fibrosis and/or immunologic reactions include pneumoconiosis, sarcoidosis, diffuse

hypersensitivity pneumonitis, Farmer's lung and bronchial asthma. This group of lung diseases is a major national health problem, second in magnitude among lung diseases only to emphysema and chronic bronchitis.

Statistical data on fibrotic lung diseases are inadequate because these diseases are difficult to diagnose and poorly reported. However, their national health impact is far greater than is generally appreciated. For example, sarcoidosis is about 12 to 15 times more common among blacks than among whites in this country, and now outranks tuberculosis as a cause of disability from pulmonary insufficiency in black populations. It is also more common in women.

Inhalation diseases are becoming more prevalent in the United States as industrialization and the technological age progress. Of all occupational illnesses, dust inhalation diseases, or pneumoconioses, are the most serious health problem. The dusts inhaled are so fine that they escape the natural cleansing mechanism of the upper respiratory tract and lodge permanently in the lungs. If exposure is sufficiently high and prolonged, the accumulated particles may cause fibrosis or scarring of the lung tissue and in many cases lead to serious disability and even death. One of the most serious problems in our country today comes from the direct handling of asbestos by some 200,000 workers and by another 3 to 5 million persons who are secondarily exposed to the dust. Asbestos is believed to be a leading factor in the deaths of over 2,000 persons each year in the U.S. The breathing of quartz dust, or silica, is another hazard which gradually causes irreversible damage to the lungs. Of the more than 125,000 workers now engaged in coal mining in the United States, an estimated 10 to 20 percent have Coal Worker's Pneumoconiosis, or "black lung." Beryllium, iron, tin, and barium dusts are also hazardous to the lung tissues.

Among immunologic lung diseases, asthma is the most common, affecting about 6 million persons in this country (approximately 3 percent of the population). It is responsible for 5 percent of all chronic disabilities and causes an annual loss of about 4 million work-days. Other immunologic lung diseases are associated with specific occupations where exposure to organic dusts or molds is high; for example, Farmer's lung in the north central states, Bagassosis among sugar cane workers in the south, and hypersensitivity pneumonitis from organisms growing in humidifiers and air conditioners. While none of these diseases is very common in the general population, their importance stems from their high incidence in particular environments.

Respiratory Failure

Respiratory failure is a complication of many nonpulmonary diseases. Acute respiratory distress syndromes have been recognized as such only recently. For these two reasons, data on incidence are not available. A conservative estimate is that 150,000 adult cases of acute respiratory distress syndrome occur each year with a mortality rate of 40 percent. These figures do not include failure due to chronic pulmonary disease, (see Emphysema and Chronic Bronchitis), nor do they adequately reflect the true incidence because so many cases are unreported.

Respiratory assistance can be provided by mechanical devices (ventilators or membrane oxygenators) that support the gas transfer functions of the lung when, as a consequence of the disease, the lungs are unable to maintain proper levels of oxygen and carbon dioxide. Ventilators are devices that mechanically inflate the lungs and can deliver increased amounts of oxygen. Membrane oxygenators are externally placed "artificial lungs" which are connected with the patient's circulatory system. Blood from the patient enters the oxygenator, carbon dioxide is removed, the blood is oxygenated and then returned to the patient's circulatory system. At present, oxygenators can only be used safely for several days. Recent experience suggests that this method of respiratory assistance holds promise for treatment of some patients in acute respiratory failure.

Pulmonary Vascular Diseases

Pulmonary vascular diseases include cor pulmonale, pulmonary hypertension, and pulmonary edema. Cor pulmonale refers to enlargement of the heart due to an increased workload of the right ventricle resulting from conditions which affect the pulmonary circulation. Pulmonary hypertension is characterized by elevation of pulmonary arterial pressure above normal levels. The condition is considered primary when found in the absence of cardiac or pulmonary diseases and secondary when associated with these diseases. Primary hypertension may be caused by factors such as high altitude and low oxygen, or ingestion of certain drugs and chemicals; secondary hypertension may result from destruction of the pulmonary vascular bed, congenital heart disease, pulmonary vasoconstriction, or congestive heart failure. Pulmonary edema, difficult to detect early, is a pathologic state in which there is abnormal extravascular storage of fluid in the lung. Reliable data on the incidence and prevalence of these diseases are not available. However, it has been estimated that cor pulmonale alone occurs in 40 percent of cases of emphysema and chronic bronchitis, both of which are chronic respiratory diseases of national impact.

Highlights of Recent Progress and Accomplishments

Lung Disease - Improved Understanding

Numerous studies are concerned with the general program of developing biological methods to separate lung cells, with particular interest focusing on isolating alveolar Type II cells and studying their principal sites of energy generation and other substructures. An extensive effort is addressed to developing cell cultures of homogeneous cell types to study cellular structure, metabolism, and function. This is an especially formidable task with regard to the lung, which has approximately 40 different types of cells, making it one of the most heterogeneous organs of the body. The biological interest in Type II cells relates to their functional role in repair of damaged epithelial cells in the lung and surfactant (pulmonary surface active material) production. These studies are important in understanding the molecular basis of lung disease.

Surfactant and its alteration seems to play a functional role in a number of lung disorders, including neonatal and adult respiratory distress syndromes, oxygen toxicity, and pulmonary edema. There also is evidence that both the activation and release of surfactant are affected by mechanical stresses such as occur during assisted ventilation.

Fundamental research on lung connective tissue and its role in lung disease has expanded dramatically. Lung collagen has been chemically characterized and found to be heterogeneous, the collagen chains resembling those isolated from other organs. When cultured, lung fibroblasts continue to synthesize collagen similar to the pattern in vivo.

A considerable amount of work is underway to elucidate the metabolic functions of the lung, which include the ability to release pharmacologically active substances, transform various biologically important blood-borne compounds, and accumulate and transform various drugs and other foreign substances. These investigations have special relevance to the control of blood pressure, and also to allergic diseases such as asthma, hypersensitivity pneumonitis, and lung diseases induced by drugs and environmental pollutants.

Respiratory Distress Syndrome - Prenatal Diagnosis

Because untreated neonatal respiratory distress syndrome has such a rapid downhill course, research on accurate early diagnosis has elicited a high level of interest. Investigators are capitalizing on the findings of fundamental

research, especially with regard to the formation and physical and chemical characterization of the surface-active material surfactant. Especially significant are two new tests that predict the degree of lung maturation from analysis of amniotic fluid.

Allergic Diseases - Improved Diagnosis

Renewed interest in the challenge technique is providing a sound pathophysiologic basis for improved diagnosis of allergic diseases. The challenge test utilizes inhaled compounds that cause a bronchial or alveolar immunologic response. Until recently, patients were challenged with unspecific compounds such as methacholine. But now specific antigens are used, permitting observations that have led to better understanding of the disease mechanisms in asthma and hypersensitivity pneumonitis.

Respiratory Failure - Diagnosis of Complications

The primary complication of respiratory failure is called hypoxic hypoxia (low oxygen content in the blood). A recently developed technique permits precise and rapid diagnosis of the several physiologic bases of hypoxic hypoxia and their relative contribution to the patient's condition. Still in a developmental stage, but being tested for resolution and validity, the technique offers great promise for therapy which can be effectively directed to the cause of the hypoxic hypoxia. Tests are being conducted at several centers and preliminary results are very encouraging.

Acute Respiratory Distress - Treatment

Continuous positive airway pressure has for some time been used with notable success to treat neonatal respiratory distress syndrome, but, until recently, the technique could only be effectively applied in centers where sophisticated technology and specially trained staff were available. The technique can now be safely used even in small hospitals or hospitals distant from large academic centers. Thus, the improved survival rates achieved by academic centers can now be anticipated in many more communities.

Artificial Lung - To Treat Respiratory Failure

Membrane oxygenators have been extensively investigated and during the last ten years a new generation of compact, disposable models that combine adequate gas exchange with minimal hematologic destruction has been developed. The principal premise for their use in the therapeutic armamentarium for acute respiratory failure is that if one can provide respiratory support and remove the threat of oxygen toxicity during the period of respiratory crisis, the lung may recover and the auxiliary oxygen support can be removed. Nine centers will participate in a randomized study to evaluate the efficacy of the membrane oxygenator in long-term respiratory support.

Device for Continuous Monitoring of Carbon Dioxide in Blood

Scientists are well on the way toward the development of instrumentation for providing continuous readouts of blood levels of carbon dioxide over prolonged periods. A device has been designed for use in conjunction with artificial blood oxygenators, now being clinically evaluated as a means of sustaining the patient during life-threatening episodes of acute respiratory failure. The device employs a length of CO_2-permeable tubing placed in the line conveying venous blood to the oxygenator. Carbon dioxide, diffusing through the tubing from the blood, is carried on a stream of nitrogen into the detector cell, which contains lithium hydroxide. Some problems still remain to be worked out, but in animal experiments, the prototype device yielded results that agreed well with blood CO_2 measurements obtained by conventional blood sampling techniques.

Blood Diseases and Resources

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$49,980,000	---	$44,350,000	---	-$5,630,000
Total	---	49,980,000	---	44,350,000	---	-5,630,000
Subactivities:						
Bleeding and clotting disorders	---	18,337,986	---	16,272,302	---	-2,065,684
Biomaterials	---	4,194,964,	---	3,722,422	---	- 472,542
Sickle Cell Disease and other disorders of the red blood cells	---	15,461,438	---	13,719,784	---	-1,741,654
Blood resources	---	11,985,612	---	10,635,492	---	-1,350,120
Total	---	49,980,000	---	44,350,000	---	-5,630,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	---	$24,961,000	---	$28,475,000	---	+$3,514,000
Competing	---	7,757,000	---	6,100,000	---	-1,657,000
Special	---	560,000	---	350,000	---	210,000
Subtotal	---	33,278,000	---	34,925,000	---	+1,647,000
Fellowships	---	1,530,000	---	1,315,000	---	- 215,000
Training Grants	---	870,000	---	527,000	---	- 343,000
Research & Development Contracts	---	14,302,000	---	7,583,000	---	-6,719,000
Total	---	49,980,000	---	44,350,000	---	-5,630,000

The 1976 estimate results in a decrease of $5,630,000 from 1975. At this level grant and contract programs in this activity would be reduced by not funding low priority noncompeting grants.

The Institute seeks to carry out a comprehensive blood program including fundamental and clinical research, professional development and training to fill projected needs, and education, prevention, and control activities to assure orderly application of the knowledge gained through research. In developing and supporting its programs in blood, the Institute seeks to use all available support mechanisms as appropriate. These include investigator initiated research projects, program project grants, goal-oriented centers such as the Specialized Centers of Research (SCOR), a National Research and Demonstration Center, targeted research and development contracts, as well as intramural support.

The National Program embraces a number of research, prevention, and education areas where interorganizational coordination is vital if effective national efforts are to succeed. The Institute also plays a key role in a number of collaborative efforts with other agencies and organizations seeking to help coordinate the many activities related to its mission. Examples of the coordination activities in blood diseases and blood resources include those in Sickle Cell Disease, Cooley's Anemia, hemophilia, hepatitis, and management of blood resources.

Major Problem Areas

The Institute's programs in blood diseases focus on bleeding and clotting disorders related to the platelets and components of blood plasma such as clotting factors, including antihemophilic factors, and on red cell disorders, particularly those related to hemoglobin, the red cell membrane and its metabolic machinery. In the case of the biomaterials program, the principal concern is the interaction of blood with artificial surfaces and ways to optimize implant materials to prevent clotting and damage to any of the components of the blood. In the blood resources program, the Institute is concerned with all constituents of blood in their roles as therapeutic agents and in the management of blood resources.

Bleeding and Clotting Disorders

Before describing the major bleeding and clotting disorders addressed in the National Program, some general principles of importance in the arrest of bleeding (hemostasis) are outlined below. The hemostatic mechanism is designed to repair breaks in the wall of small blood vessels, namely the components of the microcirculation. The microcirculation is an important part of the circulatory system. It carries to the cells of the body the materials needed for their metabolism and function and removes their waste products so that the internal environment is maintained in a manner which allows the cells to survive and perform their interrelated tasks. Bleeding and clotting in the microcirculation contribute to the adverse effects of many diseases and disorders such as hypertension, stroke, diabetes, infectious and inflammatory disease, autoimmune disease, host-graft rejection, cancer, sickle cell anemia, drug toxicity, mismatched blood transfusion, liver disease and nephritis. The impact of the bleeding and clotting diseases is vast even if it cannot be expressed statistically.

Simply stated, the hemostatic sequence involves the following steps:

- First, blood escapes from the injured blood vessel resulting in a decrease of blood pressure inside the vessel. This sets in motion a complex chain of reflexes which cause the vessel to constrict.

- Second, platelets rapidly (within one to two seconds) adhere to the irregularity in the injured vessel wall. The platelets initially attracted to the irregular site swell and release components which act as chemical messengers causing other platelets in the area to become sticky and adhere to the injured blood vessel wall. As more platelets aggregate, a temporary platelet plug is formed which achieves primary hemostatis.

- Third, as a result of the vascular injury and platelet changes, the coagulation mechanism is initiated. In a complex series of steps, a soluble component of the plasma (fibrinogen) is turned into fibrin (an insoluble protein), which forms the essential portion of the blood clot.

- Fourth, clot formation is limited to prevent occlusion of the vessel; the clot contracts to seal the lesion; and after healing has occurred, the clot is dissolved by proteolytic enzymes.

This oversimplified description of the events involved in the arrest of bleeding offers a framework for understanding how the blood vessel wall, platelets, and coagulation mechanisms are interrelated. It is important to remember that the vascular and platelet mechanisms act to achieve immediate (primary) hemostasis, and that blood coagulation is a later event (secondary hemostasis) that acts to reinforce and replace the temporary platelet plug.

Bleeding Disorders. A deficiency of hemostasis (i.e., a tendency toward bleeding) may result from a shortage of any of the plasma components required for clotting. These shortages may arise in a variety of ways. For example, since fibrinogen, prothrombin, and some other blood coagulation factors are formed in the liver, liver diseases which alter prothrombin or fibrinogen synthesis can result in excess bleeding. Excessive blood loss is a major cause of death and morbidity in a variety of circumstances such as after severe injury, after surgery, in leukemia, and in liver disease. The threat of hemorrhage limits the aggressive management of some forms of cancer. The classical hereditary condition of hemophilia results from the absence of or deficiency in antihemophilic factors. Bleeding into organs and tissues may impair or destroy their function and uncontrolled external blood loss may result.

The hemophilias are sex-linked diseases occurring almost exclusively in males. Although the known hemophilic population of this country is only about 25,000, hemophilia constitutes a major national health problem for two reasons. First, treatment must be continued throughout the lifetime of the patient at enormous cost (the current yearly cost to replace the missing clotting factor alone is estimated to be in excess of $6,000 per patient, or more than $120 million for the 80 percent of hemophiliacs who can benefit from this factor). Second, treatment of the disease presents one of the largest single demands upon the nation's blood resources.

Clotting Disorders. Thromboembolic disorders can result from one of several coagulation abnormalities including (1) presence of considerable disease of the blood vessel walls; (2) stagnation of blood flow; and (3) deficiency of naturally occurring anticoagulants within the blood. A clot which remains fixed at the initial site of injury in the blood vessel wall is called a thrombus, and the resulting condition is called thrombosis. As blood flows past the thrombus, fragments (emboli) may break loose and circulate through the vascular system.

An embolus continues to circulate until it reaches a vessel too narrow for its passage; it then becomes lodged in the blood vessel thereby occluding it. Clotting in the arteries deprives a part of the body of its blood supply; clotting in the veins impedes the return of blood to the heart. When excessive clotting affects small blood vessels and capillaries (collectively termed the microcirculation), tissues and cells cannot function well because they are deprived of essential oxygen, energy, regulating hormones and building blocks, and noxious waste products cannot be removed effectively.

The consequence of abnormal clotting depends on the organ or region of the body in which it occurs. In vessels of the heart, brain, lung, or other vital organs, the result can be catastrophic; in less vital areas, the effects may be mild and transitory. With time, the body's clot-dissolving mechanism restores the integrity of the circulation. However, the speed of this process is insufficient in the case of vital organs where even a very brief interruption of blood supply may result in irretrievable loss of function or death of tissue.

The impact of abnormal clotting is considerable. Arterial thrombosis causes or complicates a variety of diseases in all parts of the body; for example, thrombosis in the coronary arteries contributes to heart attacks, thrombosis involving the vessels of the kidney contributes to kidney failure, and arterial thrombosis and cerebral hemorrhage play major roles in stroke. Thrombosis in the veins may produce pulmonary embolism; that is, clot fragments may be carried in the blood from their site of origin to the lungs. Clotting in the venous circulation complicates many illnesses and surgical procedures. Autopsy studies show evidence of venous thrombosis in about 50 percent cases examined, regardless of cause of death, and fatal pulmonary embolism may complicate as many as one in every 1,000 major surgical procedures.

Thrombosis induced by contact of the blood with foreign surfaces remains the major unsolved problem in the development of artificial organs and prosthetic vessels or devices that temporarily assist the circulation.

Biomaterials

Biomaterials are synthetic or chemically modified natural materials which can be implanted in the body and used in a variety of biomedical applications and medical devices. To be "blood compatible", such materials must not cause damage to the various components of blood and must not induce blood to clot. In addition, biomaterials must possess specific physical properties suited for specialized functions (such as for example, gas permeability for oxygenators, suitable stiffness or elasticity in devices such as cannulae, shunts, catheters, blood pumps) and represent minimal risk of causing chemical toxicity, allergic reactions, and tumors. Several approaches are being pursued in the development of suitable biomaterials. Very promising blood compatibility was shown by specially prepared "hydrogels", a network structure of long polymer chains which contains large quantities of water. Blood compatible surfaces can be also grafted or chemically bonded to a variety of materials which have the needed physical properties, thus achieving the needed biological and physical performance. Another approach involves the use of human cells which can be grown in culture and attached to certain man-made materials to create a living interface with blood. Materials can be made which contain anticoagulants and clot-dissolving enzymes. Composite laminated materials can be produced which have directional stiffness (anisotropy) similar to natural blood vessels and heart valves, thus enabling the better functioning of replacement vessels and heart valves. Current investigations are aimed at the better understanding of the interactions between blood components and biopolymers, and their possible utilization in prosthetic devices.

Sickle Cell Disease and Other Disorders of the Red Blood Cell

The three groups of disorders considered here include Sickle Cell Anemia and Sickle Cell Trait, conditions closely related to Sickle Cell Disease such as Cooley's Anemia, and defects affecting the red blood cell membrane and its metabolic machinery.

Sickle Cell Anemia and Sickle Cell Trait. Sickle cell trait, the most common inherited blood abnormality in the United States, is believed to be carried by more than 2 million U.S. citizens, primarily blacks. However, most of these "carriers" are healthy. If two carriers marry, each of their children has a one in four chance of having sickle cell anemia, a painful and debilitating disorder affecting nearly 50,000 individuals. About one in 500 black babies in this country is born with sickle cell anemia.

Sickle Cell Anemia is a disorder characterized by the occurrence of painful "crises" which may last for hours or days, a chronic anemia related to accelerated destruction of red blood cells, and acute and chronic damage to various body organs. These clinical manifestations are caused by the presence of an abnormal hemoglobin (Hb S) leading to crescent shaped "sickled" red cells. Sickled red cells have difficulty traversing the small blood vessels and tend to occlude them. This in turn results in impaired circulation, tissue damage, and painful crises.

Sickle cell anemia, the homozygous state for the gene for Hb S (S/S disease), often causes severe and disabling symptoms and may markedly shorten life. Milder symptoms and greater longevity are encountered in certain genetic variants of sickle cell disease (Hb S-C disease, Hb S-thalassemia).

If sickling of the red cells could be altered or prevented, perhaps by a suitably designed pharmacologic agent, both the quality and duration of life for patients with sickle cell disease (a mutation which leads to the substitution of a single amino acid in one of the two kinds of polypeptide chains in hemoglobin) could be markedly improved. Much remains to be learned about the formation and structure of the aggregates of deoxygenated Hb S and the interactions of these polymers of Hb S with other red cell components. In a sense, the molecular and cellular manifestations can be considered "causes" of sickle cell disease, since the clinical manifestations are based upon the molecular and cellular phenomena.

The cost of caring for a patient with sickle cell disease may approach $2,500 to $5,000 per year. The loss of time from school and jobs, and the resultant psychological and educational problems, make this disorder one of high social and economic impact.

Cooley's Anemia.

Cooley's anemia (thalassemia) results from defective production of one of the subunits of the hemoglobin molecule, leading to rapid destruction of the red cells. It occurs in perhaps 5,000 Americans, largely of Mediterranean ancestry. Its victims suffer profound anemia and require repeated blood transfusions for survival. As with the sickle cell trait, most carriers do not have symptoms, but one in four offspring may be affected if two carriers marry.

Membrane and Enzyme Defects

Defects in red cell membranes and red cell enzymes also produce anemia by causing premature destruction of the red blood cells. Such defects are relatively rare, except one, called glucose-6-phosphate dehydrogenase deficiency (G6PD), which occurs in about 10 percent of black males and less frequently in males of Mediterranean ancestry and in other populations. Most of these individuals are healthy, but may develop anemia with certain illnesses or if they take a variety of commonly used drugs.

Blood Resources

Safe and adequate supplies of blood must be available for the nation. Most whole blood is collected by an assemblage of organizations which might be referred to as the blood service complex. As stated earlier, whole blood contains red blood cells, white blood cells, and platelets suspended in plasma. About 9 million units of whole blood and another 8.5 million unit equivalents of blood plasma are collected and used for therapy in the United States each year. The optimal management and utilization of this national resource is vital to the improved health care of the nation.

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Transfusion of red blood cells is important in restoring the normal oxygen-carrying capacity of the blood in patients acutely anemic as a result of hemorrhage or chronically anemic because of diseases interfering with normal red-cell production. Of all the blood components used in transufsion therapy, red cells are needed in the greatest quantity. White blood cells are vital to the body's defense against infection. In cancer, leukemia, and certain allergic states, circulating leukocytes are frequently diminished in quantity or impaired in functional quality. As a result, the patient is susceptible to serious infections that may not respond to antibiotic treatment. Transfusions of white blood cells may be beneficial in such cases. Platelets play a prominent role in the initiation of coagulation, and in the maintenance of the blood vessel integrity. Leukemia patients often have low circulating platelet levels, either as a result of the disease itself or as a toxic reaction to the drugs used in treating their disease. Drug treatment of solid tumors also frequently reduces platelet levels. Such platelet deficiencies can result in serious, often fatal hemorrhage. Platelet transfusions are vital for these patients.

Approximately 1.7 million liters of plasma are collected each year, mainly for the preparation of plasma protein fractions such as serum albumin used to treat shock; blood grouping protein needed for blood typing; gamma globulin for antibodies to fight disease; and antihemophilic globulin to allay bleeding in hemophiliacs.

Highlights of Recent Progress and Accomplishments

Blood Diseases--Improved Understanding. Scientists have developed cell-free systems for protein synthesis that faithfully duplicate in the test tube both normal hemoglobin synthesis and the disturbances in hemoglobin production responsible for such hereditary blood disorders as Cooley's anemia and sickle cell disease. The system permits the various components involved in hemoglobin production to be manipulated at will. This, in turn, makes it possible to study the contribution of each component to the production of regulatory processes, to identify the causes of various hemoglobin disorders, to define the nature of defects, and to seek out and evaluate potential approaches to the correction or amelioration of associated clinical disease problems.

Cooley's Anemia--Improved Understanding. In Cooley's anemia, the scientists have found that the basic defect is a relative shortage in red blood cells of the genetic material, called betaglobin mRNA, that directs the assembly of one of the two protein chains that are combined to form the hemoglobin molecule. As a result of this shortage, beta-chain synthesis is much slower than usual, while alpha-chain synthesis proceeds at a normal rate. The result is a large excess of alpha chains, which eventually precipitate in the red blood cell and cause it to be destroyed long before it has lived out its normal life span. Hence, persistent anemia results and can currently be corrected only by periodic blood transfusions. Now that the basic defect in Cooley's anemia has been identified, scientists are seeking possible means of stimulating increased beta-globin mRNA synthesis during the initial production of red blood cells, which might correct the imbalance between alpha- and beta-chain production that is the underlying cause of this blood disorder.

Blood Diseases--Improved Understanding. In two major hereditary blood diseases--Cooley's anemia and sickle cell disease--the problem resides in the beta-chain of hemoglobin. In Cooley's anemia, beta-chain production is abnormally slow; in sickle cell disease, the beta chain is flawed. Both abnormalities have serious clinical consequences for the victim. Humans have the genetic capability to produce more than one kind of hemoglobin. The hemoglobin found in fetal red blood cells (hemoglobin F) in contrast to that in adults (hemoglobin A) does not contain the beta chain. Hemoglobin F is a perfectly serviceable form of hemoglobin, but a genetic switch to hemoglobin A production normally occurs shortly after

birth. In goats and certain species of sheep, three forms of hemoglobin F, an intermediate form called hemoglobin C, and hemogobin A. A genetic switch from hemoglobin A to hemoglobin C production can be achieved by making the animals anemic. This can also be done in a limited way in the test tube by exposing bone marrow cells to high concentrations of the hormone erythropoeitin. The mechanisms of this genetic switching are under study as are various agents that might induce a switch in production from one form of hemoglobin to another. Similar studies are planned with human marrow cells to determine whether these cells can be induced to switch from adult to fetal hemoglobin synthesis. Activation of hemoglobin F synthesis in the cells of subjects with sickle cell disease or Cooley's anemia, by eliminating the beta-chain problems resulting from these disorders, might well alleviate the symptoms of these diseases.

Sickle Cell Disease--Screening and Education Clinics. To reduce the painful, crippling, and possible life-threatening effects of sickle cell anemia, the Institute supports screening and education clinics administered by the Sickle Cell Disease Office, Bureau of Community Health Services, Health Services Administration. This program serves to develop and field test methods of carrying out service activities, including public awareness, education screening, counseling, and patient referral under various circumstances in a variety of environments. During the past year some 26 screening and education clinics were in operation. During that period approximately 400,000 individuals were screened for evidence of sickle cell disease, and approximately 1 in 10, or 40,000 were found positive and were given appropriate counseling on the nature of the disease and were referred to appropriate services. In addition, the Comprehensive Sickle Cell Centers supported by Institute grants have screened over 100,000 individuals, of whom approximately 10,000 were counseled and referred to appropriate services.

Sickle Cell Disease--Diagnosis and Treatment. To successfully combat the effects of sickle cell disease, there is a need to provide more accurate, less expensive, and less time consuming methods to identify normal hemoglobins in patients being screened. Preliminary studies using microcolumn chromatography procedures suggest that this approach may provide a useful, quick, and accurate tool for the identification of sickle and several other abnormal hemoglobins. The early identification of eye lesions and their treatment may significantly reduce blindness and other visual complications in sickle cell disease. New photographic contrast techniques have been developed to better detect such lesions and various modifications of treatment, including argon and xenon photocoagulation, are currently underway.

Blood Clots--Detection. Several promising new assays have been developed to detect blood clots in the blood vessels. One is based on the detection of clot formation degradation products in the blood through radioactive tagging; others involve combinations of radioactive labeling of blood proteins, blood flow measurements, and special labeling of blood proteins, and special X-ray procedures. These assays should provide potential tools for the detection and quantitation of intravascular clot formation and its localization.

Blood Clots--Treatment and Prevention. Venous thrombosis (blood clots in the veins) is a frequent complication in patients undergoing orthopedic surgery. Current clinical trials will determine the effectiveness of heparin and platelet-inhibitor drugs in preventing venous thrombosis and will also determine the high-risk populations that might benefit most from such treatments.

National Blood Banking. Recently completed and published reports of a blood resource study on cost finding methodology adaptable to the blood banking community can now form the basis for establishing a uniform, rational policy for determining costs throughout the nation.

Blood Banking--Information System. A recently published report from the blood resources studies on the analysis and design for a national blood resource information system based on standardized reporting which is applicable to the blood banking community of the nation is being used as the basis for the implementation of such a national blood banking data system to be established through the Bureau of Biologics of the Food and Drug Administration in collaboration with the Institute.

Safety of Blood Therapy. Studies on the removal or inactivation of hepatitis B virus from blood derivatives prior to transfusion indicate that it may be possible to render prothrombin complex preparations hepatitis-free. If these techniques are successfully applied to these and other blood derivatives, the risks of hepatitis following transfusion may be significantly reduced.

Frozen Blood--Improved Utilization. The development of a closed system docking device for use with thawed-frozen blood transfusion preparations is now at the stage of clinical testing prior to licensure by the Food and Drug Administration for use in the nation's blood system. Successful use of such sterile connecting devices should allow extended lifetime of such thawed preparations and thus reduce wastage of valuable blood resources due to outdating of these preparations before they can be transfused.

Transplantation Graft Rejection. A contributory role in graft rejection by transplant patients appears to include pre-sensitization to transplantation antigens as a result of blood transfusions. Preliminary evidence from Institute-supported clinical studies indicate that transplantation related (HL-A) antigen conversions are less likely to occur in such patients receiving frozen blood than those receiving leukocyte-poor (low numbers of white blood cells) blood prepared by centrifugation.

Biomaterials--Development and Evaluation. Two promising synthetic membranes (a flourinated cellulose, and a polyalkylsulfone) have been developed for use in oxygenators. Special technological procedures enabled the preparation of synthetic laminates having mechanical stiffness ratio (anisotropy) similar to natural leaflet heart valves. This particular property is of paramount importance in the regulation of blood flow and in assuring the durability of the heart valves. Very thin carbon coatings were successfully deposited onto flexible synthetic materials, thus making the latter blood compatible. It has been shown and confirmed that when materials are in contact with blood, the immediate first reaction is the absorption of plasma proteins. Only after the deposition of some plasma proteins has occured, will the formed blood elements, especially the platelets come into contact with the proteinated surfaces. Consequently, the study of the initial events of protein absorption is of great significance for the understanding of blood compatibility and for the design of better materials. Among the synthetic materials that seem to take up the least proteins when in contact with blood are some specially prepared "hydrogels."

Intramural Laboratory and Clinical Research

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	387	$8,745,000	370	$9,240,000	-17	+$495,000
Other expenses	---	15,638,000	---	15,459,000	---	-179,000
Total	387	24,383,000	370	24,699,000	-17	+316,000

The Bethesda-based laboratories and branches of the NHLI intramural research program conduct a variety of basic and clinical studies on the cardiopulmonary system and the diseases that afflict it. The budget provides for essentially the same level of activity in 1975 and 1976. The dollar change indicated is for "built-in" increases such as within-grade pay increases, annualization of pay raises, etc.

Within the framework of seeking fundamental knowledge of disease processes, basic studies comprise a significant portion of the program. Such studies range from study of the subtle biochemical mechanisms controlling the central and autonomic nervous systems to a study of the basic functioning of the primitive cell. The balance and major portion of research is directed specifically toward a solution to the various forms of cardiovascular distress. Because of the recognized excellence of its programs, the Institute also attracts many trainees, who, after accelerated and intensive training, return far better equipped for service in the medical and scientific communities.

The Institute has 370 positions for this activity, of which about half are for scientists and physicians and the remainder for technical personnel. Basic and clinical research was carried on in 13 major laboratories and branches through 317 projects in 1974. One hundred hospital beds are at the disposal of the clinical program. Support is given also to a vigorous out-patient clinical program with approximately 5,000 patient visits annually.

Highlights

Lung Diseases

The Institute has long been recognized for the excellence and productivity of its cardiovascular laboratories. Until 1972 the Institute had not engaged in pulmonary research. Primary goals for the new lung program were to understand the composition of collagen in animal and human lungs; to develop *in vitro* systems to study the synthesis of collagen in the lung; and to develop animal models of lung growth.

Collagen is a major constituent of the connective tissue "cement" that binds together the cellular components of organs and tissues. It is the most abundant protein in the lung, comprising 10 to 15 percent, by weight, of normal lung tissue in adults. Lung connective tissue figures prominently in a number of pulmonary disorders. In the so-called interstitial lung diseases, which account for about 20 percent of chronic lung conditions, a major factor appears to be excessive collagen and connective-tissue production and subsequent development throughout the lung of fibrous tissue that interferes with normal respiratory function. Conversely, in emphysema and related disorders, the problem appears to be the breakdown or denaturation of collagen or other connective tissue components, with subsequent disruption of the functional units of the lung (alveoli) where gas exchange occurs.

NHLI studies are concerned with learning more about collagen production in the lung and about the mechanisms that control the process. The ultimate goal is discovery of means whereby excessive connective-tissue proliferation might be halted or slowed down to prevent fibrosis in interstitial lung diseases or whereby the synthesis of functional alveoli might be stimulated in order to replace those lost to emphysema and related diseases.

The studies indicate that the lung produces as many as five different forms of collagen, three of which have been characterized. One of these resembles the collagen of cartilage, a second the collagen of skin, and a third the collagen found in the aorta and, possibly, other major arteries.

During fetal development, collagen production accounts for about 3 percent of total protein synthesis in the lung. During the new-born period, this figure rises to 14 percent and the collagen concentration in lung tissue increases, indicating a shift of emphasis in lung protein synthesis toward collagen production. By adulthood, collagen synthesis has returned to the 3 percent level of late-fetal development and there is no further accumulation of collagen in the lung. The NHLI studies are attempting to define the mechanisms by which collagen synthesis is "turned on" during the period of maximal lung development, then gradually "turned off" as the lungs attain maturity.

An animal model in current use is young rabbits in which one lung is surgically removed, after which the remaining lung roughly doubles in size within one month. (Again, the rate of collagen synthesis increases, though without any increase in per unit lung-collagen concentration). Another model is a cell-free system in which the cellular components required for the synthesis of collagen and other lung proteins are extracted from homogenized lung tissues of various origins, then combined in varying proportions to synthesize collagen in the test tube. Finally, enzymatic techniques have been developed for breaking down the connective tissue framework of lung tissue, so that individual cells are dispersed into appropriate media, whence the various cell types (up to 40 in the normal lung) may be segregated, harvested, and then grown in culture to determine their role (if any) in collagen synthesis and to assess the effects (if any) of various chemical stimuli on the rate of synthesis.

The connective tissue of lung is often involved in human pulmonary disease. Fuller understanding of the processes involved in connective tissue synthesis and destruction may lead to therapeutic measures to stimulating the repair or regeneration of lung tissue damaged or destroyed by emphysema and related lung disorders or to measure s for preventing or slowing down the lung fibrosis resulting from other lung disorders.

Blood oxygenators, the "lungs" of heart-lung machines used in cardiovascular surgery, also hold considerable promise in the treatment of acute respiratory failure. The most promising oxygenator for this purpose is the membrane oxygenator. Its gentle blood-handling characteristics make it suitable for providing respiratory assistance over prolonged periods--up to a week or more in several reported instances--by which time many acute respiratory crises have run their course.

NHLI scientists have developed methods for casting very thin membranes without the pinhold defects that have been the chief cause of membrane failure in oxygenators. Flowless silicone rubber membrane less than one thousandth of an inch thick can be produced by this technique. The defect-free membranes have been incorporated into a spiral-coil membrane oxygenator developed at NHLI. In experiments in sheep, they have shown excellent gas-exchange and blood-compatibility characteristics during prolonged periods of blood oxygenation.

Research will continue on the development of membrane combining high gas-exchange efficiencies with blood compatibility. The goal is a compact membrane oxygenator that can provide safe and reliable respiratory support for whatever

length of time is necessary to see the patient through an acute respiratory crises.

Coronary Heart Disease--Arrhythmias

The slowed heart rate that often occurs in the wake of an acute heart attack has been considered a dangerous complication by most clinicians, who often administer atropine to speed up the heart when its rate falls below 60 beats per minute. Atropine increases heart rate by depresssing the cardiac vagal nerves that normally act as a brake on heart rate. But recent NHLI studies indicate that the increased vagal tone and decreased heart rate after an attack may, in fact, help to protect the heart against serious aberrations in heart rhythm and against the uncoordinated, ineffectual contractions of the ventricles called ventricular fibrillation, an often lethal complication of acute heart attacks.

The protection against arrhythmias resulting from increased vagal tone appears to be mediated by acetylcholine, a chemical messenger or neurohormone released in heart muscle from vagal nerve endings. Subsequent animal studies have indicated that the electrical stability of blood-deprived or damaged heart muscle could be increased by drugs that slow the enzymatic destruction of acetylcholine released by vagal stimuli. The scientists believe that this pharmacological approach holds promise for the prevention of arrhythmias during the critical period after an acute heart attack.

Further investigation is needed to define the potential advantages and limitations of measures to maintain or increase cardiac vagal tone in protecting the heart from arrhythmias that pose a serious three after acute heart attacks.

Heart Failure and Shock

Clinical studies are in progress to evaluate the effectiveness of nitroglycerin alone or nitroglycerine plus phenylephrine in reducing ischemic heart-muscle damage, arrhythmias, and other potential complications of acute heart attacks. The extent and severity of heart-muscle damage resulting from a heart attack is often a crucial factor affecting survival and also the amount of residual disability after recovery. Arrhythmias remain a significant cause of death during the critical phase after acute heart attacks. Herein lies the potential importance of clinical studies that may define a new application for one of the oldest cardiac drugs.

Hypertension

Research has indicated that blood pressure levels, the output of various hormones and vasoactive substances, and urinary excretion of sodium and potassium rise and fall rhythmically in cycles lasting approximately 24 hours (circadian rhythms). These rhythms vary from one individual to the next and are subject to modification by such factors as changes in the diet (especially sodium intake), stress, sleep-wake schedules, and geographical displacement. Because a number of factors involved in blood pressure regulation are subject to circadian variation, these rhythms cannot be ignored in research concerned with possible causes of hypertension. Fuller understanding of these rhythms is also relevant to treatment of the disease so as to maximize the effectiveness of drug therapy while reducing the incidence and severity of undesirable side effects.

The kallikrein-kinin system is believed to play important roles both in blood-pressure regulation and in kidney function. Kallikreins are protein-digesting enzymes produced in the kidney and various exocrine glands. These enzymes, in turn, regulate the production in the blood of kinins, the most powerful blood vessel dilators known. Results thus far suggest that the kallikrein-kinin system is an important factor in blood-pressure control, and probably interacts with the renin-angiotensin-aldosterone system and possibly others in various hypertensive states. A fuller understanding of the kallikrein-kinin system may shed new light

on mechanisms of blood pressure regulation and on derangements that underlie primary hypertension and various secondary forms of the disease.

Congenital and Rheumatic Heart Diseases

NHLI studies show that echocardiography is a painless, safe, noninvasive technique for visualizing the heart and great vessels by means of reflected ultrasound. It is proving to be extremely useful in the diagnosis and evaluation of a variety of congenital and acquired heart conditions.

Echocardiography is also uniquely valuable in the diagnosis of assymetrical septal hypertrophy (ASH), a genetically transmitted disease of heart muscle. In all cases of ASH, the ventricular septum is thickened, especially in the vicinty of the aortic valve, through which all blood destined for the systemic circulation must pass.

Studies now in progress indicate that ASH may become clinically manifest in infancy, may be a factor in sudden infant death, or may lead to heart failure and death in the early months of life. It seems likely that ASH may be more common than generally supposed, since non-obstructive ASH is often difficult to detect by techniques other than echocardiography, whose potential in cardiovascular diagnosis is only beginning to be realized. Continued clinical evaluation of echocardiography may result in widespread use of what appears to be an extremely powerful tool for the diagnosis and evaluation of a variety of cardiovascular disorders.

Also, in rheumatic heart disease, studies in progress are directed toward defining the mechanisms underlying the reduction in ejection fraction that bodes ill for some patients with aortic regurgitation and to determine whether measurements of left ventricular volume and ejection fraction are a more sensitive means of determining the optimal time for aortic valve replacement than are the traditional clinical parameters.

Cooley's Anemia

Like all species of RNA that direct the synthesis of cellular proteins, alpha-globin mRNA and beta-globin mRNA are produced by the genetic material DNA; and so the molecular defect in Cooley's anemia appears to be faulty regulation in the synthesis of a gene product. Studies now in progress are concerned with defining the nature of this flaw and seeking potential means of correctin the alpha/beta chain imbalance responsible for the clinical problems of Cooley's anemia by more direct means than periodic red-cell replacement.

Research Management and Program Services

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	324	$7,156,000	321	$7,571,000	-3	+$415,000
Other expenses	---	9,973,000	---	10,007,000	---	+34,000
Total	324	17,129,000	321	17,578,000	-3	+449,000

This activity provides support for the Institute Director and his immediate staff (including the Office of Prevention, Control, and Education, the Office of Administrative Management, and the Office of Program Planning and Evaluation) and for professional direction and administration of the Institute's grant and contract programs. All of the staff of the Institute, with the exception of its intramural laboratory and clinical scientists and technical staff, are funded from this activity.

Funds support the overall direction, coordination, planning, administration, and information activities of the varied programs of the Institute. The Director and his immediate staff are responsible for introducing new knowledge into current operating programs and for planning, development, and review of new areas of focus and interest. Funds also provide for scientific and administrative direction of grant and contract programs.

The 1976 budget provides for three fewer positions than in 1975. The requested increase is for "built-in" changes such as within-grade pay increases, annualization of pay raises, etc.

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Heart and Vascular Diseases. (Public Health Service Act, Section 301, Title IV, Part B, and Title XI)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$187,777,000	1/	---	$166,578,000

Purpose: This activity, through the Division of Heart and Vascular Diseases, represents a response to the mandate of the National Heart, Blood Vessel, Lung, and Blood Act, and includes detection, diagnosis, treatment and preventive programs. In the Act, the Institute is mandated to conduct research programs including investigations of the epidemiology and etiology of heart and blood vessel diseases and studies of the basic biological mechanisms and processes involved in normal and abnormal phenomena. The array of current and long-range opportunities and needs for advancement is impressive and expanding. The National Program is conducted through 10 program areas: arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, peripheral vascular diseases, arrhythmias, heart failure and shock, congenital and rhematic heart diseases, cardiomyopathy and infections of the heart, and circulatory assistance.

Explanation: In response to the enabling legislation, the National Heart and Lung Institute continues to develop and support an integrated program embracing fundamental and clinical research, manpower development and training to satisfy projected needs. It supports prevention, control, and education activities to provide for efficient and timely application of knowledge obtained through research.

Accomplishments in 1975: An intensive program has been launched to develop and assess new and improved instrumentation and techniques for noninvasive detection, characterization, and quantification of atherosclerosis. In improved diagnosis of heart disease, a new diagnostic technique called echocardiography has been developed. Work has continued on improved detection of risk factors in heart attacks and their standardization. There has been improved dietary data collection in the relationship of diet to heart diseases. In the prevention of premature heart disease, the continent-wide network of Lipid Research Clinics will complete patient enrollment during calendar 1975. This is a study to determine whether reducing blood cholesterol levels in patients with Type II hyperlipoproteinemia can slow down or prevent the development of premature coronary artery disease. The purpose of the Multiple Risk Factor Intervention Trial (MRFIT) is to determine whether or not a preventive program directed at a reduction of elevated blood lipids (cholesterol), reduction of high blood pressure, and reduction or elimination of cigarette smoking will result in a significant reduction in deaths from coronary heart disease. Out of a massive screening effort, the enrollment goal of 12,000 is expected to be reached during calendar 1975. Clinical evaluation in heart attack patients is being done on the effects of nitroglycerin. Thus, one of the oldest and best drugs for relieving chest pain of angina pectoris, also may be valuable in the treatment of acute heart attacks. An expanded program was launched in studies designed to quantify the amount of heart muscle damaged during a heart attack. Thirty clinical centers, a coordinating center, and an ECG reading center have been selected for the Aspirin-Myocardial Infarction Study. Pilot phase studies of coronary artery bypass surgery were initiated preparatory to a full-scale collaborative trial. The Institute implemented a program of Specialized Centers of Research on Ischemic Heart Disease. The

Heart and Vascular (Continued)

objectives of this program is multidisciplinary clinical and fundamental research directed at the reduction of death and disability from all forms of ischemic heart disease. The National High Blood Pressure Education Program reached the stage of becoming fully operational and research was initiated last spring on new methods of educating the public and professionals about hypertension. The Hypertension Detection and Follow-Up Program (HDFP) completed screening to enroll its goal of over 10,000 persons in a program to assess the ability of a program of long-term antihypertensive therapy to reduce mortality and morbidity from high blood pressure. Continued research was conducted on the behavioral aspects of persons with high blood pressure and on possible side effects of therapy. Progress continues to be made in developing materials, components, and systems for circulatory assist and cardiac replacement or artificial heart devices.

Objectives for 1976: The Institute will continue to support high priority programs in heart and vascular research.

1/ Authorization expires June 30, 1975.

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Lung Diseases (Public Health Service Act, Section 301, Title IV, Part B, and Title XI)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$44,615,000	1/	---	$39,589,000

Purpose: This activity, conducted by the Division of Lung Diseases, is responsible for overall planning, coordination and evaluation of all extramural activities relative to respiratory diseases.

Explanation: Research programs range from studies concerned with the fundamental mechanisms of lung cell metabolism to the development of instrumentation for ventilatory assist and rehabilitation. The scope of research is large as dictated by the diversity of the disease mechanisms of the lung.

Accomplishments in 1975: Progress has been made in fundamental studies to elucidate lung disease mechanisms: four new multidisciplinary programs that emphasize correlation of lung structure and function were initiated. Because untreated neonatal respiratory distress syndrome has such a rapid downhill course, research on accurate early diagnosis elicited a high level of interest. Emphasis continued on efforts to identify the risk factors and genetic basis for chronic obstructive pulmonary diseases such as emphysema and chronic bronchitis. Significant advances in the early detection of asthma, an immunological disease, have been achieved through the methacholine inhalation challenge technique. This test identifies individuals with asthma before it is clinically apparent. Techniques and devices have been developed for detecting impending respiratory failure. A new multiple inert-gas technique has been developed that measures the uneven distribution of ventilation-perfusion in the lung. The resolution and sensitivity of this method is sufficient to identify local gas exchange abnormalities in experimental animals before these can be detected by routine pulmonary function measurements. An educational program was initiated to disseminate information about current techniques for early identification and treatment of acute respiratory insufficiency. Prototype techniques have been developed to study early water accumulation in pulmonary edema. The measurement of abnormal accumulation of lung water, by using insoluble inhaled gases, is noninvasive and may be performed in acutely dyspneic patients. This new approach is now at the stage of clinical evaluation. Major progress continues in the development and testing of membrane oxygenators in animals and in man.

Objectives for 1976: The Institute will continue to support high priority programs in lung research.

1/ Authorization expires June 30, 1975.

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Blood Diseases and Resources (Public Health Service Act, Section 301, Title IV, Part B, and Title XI)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$49,980,000	1/	---	$44,350,000

Purpose: This activity, conducted by the Division of Blood Diseases and Resources, plans and directs research on blood diseases and blood resources within the National Program which seeks to be responsive to the 1972 legislative act which specifies "Studies and research into blood diseases and blood, and into the use of blood for clinical purposes, and all aspects of the management of its resource in this country." The program deals with bleeding and clotting disorders, biomaterials, sickle cell disease and other disorders of the red blood cell, and blood resources.

Explanation: The Institute seeks to carry out a comprehensive program including fundamental and clinical research, professional development and training to fill projected needs, and education, prevention, and control activities to assure orderly application of the knowledge gained through research.

Accomplishments in 1975: Specific clotting factors, lacking or inactive in the hemophiliac have been identified, partially characterized and can now be separated commercially from normal donor plasma. These research advances, coupled with a more sophisticated management of our national blood resource, promise to make better products for the treatment of this disease more widely available at less prohibitive costs. A number of clinical situations with a high risk for thrombosis and embolism have been identified. Improved biomaterials suitable for several uses have been produced by surface grafting and bonding processes. The possibility of developing blood compatible living cell surfaces by tissue culture techniques presents an alternative to synthetic materials. Work progressed in basic research aimed at assessing the changes in blood components that result from their contact with natural and synthetic surfaces. Conversely, the changes in biomaterials produced by contact with blood are also being studied. Fundamental research in sickle cell disease continues to advance our understanding of this disorder. Programs were developed to expand the dissemination of information about the disease and provide continuing education for physicians and related health personnel. Progress continues in our understanding of the red cell, its membranes, its enzyme systems, and the properties which contribute to the cell's visibility and proper physiologic functions in the circulation. Several studies were recently completed on the development of a Nationwide Blood System.

Through the cooperative efforts of NHLI and several other agencies, comprehensive prospective epidemiologic studies of post-transfusion hepatitis are being carried out. New methods of plasma fractionation continue to be explored in an attempt to find more efficient and economical methods of producing blood derivatives.

Objectives for 1976: The Blood Diseases and Resources program will continue to support studies and research to support the goals and implementation of the National Blood Policy.

1/ Authorization expires June 30, 1975.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Intramural Laboratory and Clinical Research. (Public Health Service Act, Section 301, Title IV, Part B, and Title XI)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
	$24,383,000	1/	370	$24,699,000

Purpose: This is a research program within the facilities of the NIH at Bethesda. Within the framework of seeking fundamental knowledge of disease processes, basic studies comprise a significant portion of the program. Such studies range from study of the subtle biochemical mechanisms controlling the central and autonomic nervous systems to a study of the basic functioning of the primitive cell. The balance and major portion of research is directed specifically toward a solution to the various forms of cardiovascular, pulmonary, and blood diseases.

Explanation: The Institute has 370 positions from this activity, of which about half are for scientists and physicians and the remainder for technical personnel. Basic and clinical research is carried on in 13 major laboratories and branches through 317 projects in 1974. One hundred hospital beds are at the disposal of the clinical program. Support is given also to a vigorous out-patient clinical program with approximately 5,000 patient visits annually. Because of the recognized excellence of its programs, the Institute also attracts many trainees, who, after accelerated and intensive training, return far better equipped for service in the medical and scientific communities.

Accomplishments in 1975: The Institute has long been recognized for the excellence and productivity of its cardiovascular laboratory and clinical research. Until 1972 the Institute had not engaged in pulmonary research. During the past year the preliminary primary goals for the new lung program were attained. These were an understanding of the composition of collagen in amimal and human lungs; to develop in vitro systems to study the synthesis of collagen in the lung; and to develop animal models of lung growth. Other recent advances include the evaluation of pharmacological approaches to arrthymias; clinical studies to evaluate the effectiveness of nitroglycerine alone or nitroglycerine plus phenylephrine in reducing ischemic heart-muscle damage, arrhythmias, and other potential complications of acute heart attacks; the elucidation of a number of factors involved in blood pressure regulation; advances in echocardiography, which is a painless, safe, noninvaseive technique for visualizing the heart and great vessels by means of reflected ultrasound; progress in defining genetic flaw factors which result in molecular defects which result in such diseases as Cooley's anemia.

Objectives for 1976: The Institute will continue its in-house research programs.

1/ Authorizing legislation expires June 30, 1975.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Research Management and Program Services. (Public Health Service Act, Section 301, Title IV, Part B, and Title XI)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
328	$17,129,000	1/	321	$17,578,000

Purpose: This activity provides the support necessary for the overall management of the Institute. Included within this activity are: the Director and his immediate staff (including the Office of Prevention, Control, and Education, the Office of Administrative Management, and the Office of Program Planning and Evaluation), and the staffs of the program divisions and the Division of Extramural Affairs, who provide the professional direction and administration of the Institute's grant and contract programs.

Explanation: Funding for this area provides for salaries and other operating costs for the overall direction, coordination, planning and administration activities of the Institute. All of the Institute staff, with the exception of the Intramural laboratory scientists and technical staff, are funded from this activity.

Accomplishments in 1975: In 1975 continued leadership was provided for an accelerated National Program authorized in the National Heart, Blood Vessel, Lung, and Blood Act of 1972. The purpose of the plan was to "expand, intensify, and coordinate the activities of the Institute respecting heart, blood vessel, lung, and blood diseases..." The Institute has forwarded the Second Annual Report of the National Heart and Lung Advisory Council and has prepared the Second Annual Report of the Director of the National Heart and Lung Institute for transmittal to the Congress of the United States. The Institue established the first three National Research and Demonstration Centers in 1975, one in each of its principal categorical areas. It is continuing the phased implementation of large-scale clinical trials in arteriosclerosis, hypertension, and myocardial infarction which will involve hundreds of thousands of people in this nation. It initiated the Aspirin-Myocardial Infarction Study; patient enrollment is expected to be completed by the end of calendar 1975. The National High Blood Pressure Education Program reached the stage of becoming fully operational. The Pulmonary Academic Award program was expanded and the Young Pulmonary Investigation award program was initiated. The Secretary of HEW approved the establishment of an American Blood Commission through which the private sector in blood banking will develop and submit plans for implementation of the National Blood Policy.

Objective for 1976: The Institute will continue the management and direction of its research programs.

1/ Authorization expires June 30, 1975.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

National Heart and Lung Institute

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$292,794,000	$59,715,000
Total Obligations	292,794,000	59,715,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Heart and vascular diseases.....	---	$166,578,000	---	$32,800,000
Lung diseases.....	---	39,589,000	---	7,950,000
Blood diseases and resources.....	---	44,350,000	---	8,950,000
Intramural laboratory and clinical research.....	370	24,699,000	370	6,378,000
Research management and program services...	321	17,578,000	321	3,637,000
Total obligations..	691	292,794,000	691	59,715,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions....	691	691
Full-time equivalent of all other positions.....	80	80
Average number of all employees.....	754	754
Personnel compensation:		
Permanent positions.....	$13,531,000	$3,350,000
Positions other than permanent.....	1,100,000	300,000
Other personnel compensation.....	475,000	130,000
Subtotal, personnel compensation...	15,106,000	3,780,000
Personnel benefits.....	1,705,000	400,000
Travel and transportation of persons...	747,000	100,000
Transportation of things.....	100,000	10,000
Rent, communications, and utilities....	800,000	150,000
Printing and reproduction.....	550,000	75,000
Other services:		
Project contracts.....	63,828,000	8,000,000
NIH Management Fund.....	13,569,000	4,115,000
Other.....	5,100,000	585,000
Supplies and materials.....	3,700,000	650,000
Equipment.....	900,000	150,000
Grants, subsidies, and contributions...	186,689,000	41,700,000
Total, obligations by object.....	292,794,000	59,715,000

Narrative

The estimate for the three-month interim period reflects a continuation of the programs of the National Heart and Lung Institute consistent with the 1976 Estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

Program Activities

The mission of the National Heart and Lung Institute is to provide leadership for a National Program in diseases of the heart, blood vessels, lungs, and blood, and in blood resources. The NHLI is responsible for the following activities:

Provides leadership for a National Program in diseases of the heart, blood vessels, lungs, and blood; plans, conducts, fosters, and supports an integrated and coordinated program of research, investigations, clinical trials, and demonstrations relating to the causes, prevention, methods of diagnosis and treatment (including emergency medical treatment) of heart, blood vessel, lung, and blood diseases through research performed in its own laboratories and through contracts and research grants to scientific institutions and to individuals; plans and directs research in the development, trial, and evaluation of drugs and devices relating to prevention and treatment, and the rehabilitation of patients suffering from such diseases; conducts studies and research into the clinical use of blood and all aspects of the management of its resources; supports training of manpower in fundamental sciences and clinical disciplines for participation in basic and clinical research programs relating to heart, blood vessel, lung, and blood diseases by training grants and fellowships; coordinates with the other research institutes and with all Federal health programs, relevant activities in the above diseases, including the related causes of stroke; conducts educational activities, including the collection and dissemination of educational materials on these diseases, with emphasis on the prevention thereof, for health professionals and the lay public; maintains continuing relationships with institutions and professional associations and with international, state and local officials, and with voluntary agencies and organizations working in these areas.

FRIDAY, APRIL 11, 1975.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. SEYMOUR J. KRESHOVER, DIRECTOR
DR. RONALD LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DR. CLAIR L. GARDNER, ASSOCIATE DIRECTOR, EXTRAMURAL PROGRAMS, NATIONAL INSTITUTE OF DENTAL RESEARCH
JOHN P. PATTERSON, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH
MRS. FRANCES H. PETTINATO, FINANCIAL MANAGER, NATIONAL INSTITUTE OF DENTAL RESEARCH
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We will continue with the National Institutes of Health. Now we have the National Institute of Dental Research.

The presentation will be made by Dr. Seymour Kreshover.

We have a biographical sketch of you, Doctor, which we will place in the record at this point.

BIOGRAPHICAL SKETCH OF DR. SEYMOUR J. KRESHOVER

Name, Seymour J. Kreshover.

Position, Director, National Institute of Dental Research, NIH; Assistant Surgeon General, PHS.

Birthplace and date, New York, N.Y., June 22, 1912.

Education: B.A., New York University, 1934; D.D.S., University of Pennsylvania, 1938; Ph. D., Yale University, 1942; M.D., New York University, 1949.

Experience: Director, National Institute of Dental Research, NIH, 1966 to present; Scientific Director, National Institute of Dental Research, NIH, 1956-66; Associate Trustee, Board of Medical Education and Research, University of Pennsylvania, 1956-60; Professor of Oral Pathology, Director of Dental Research, Director of Graduate and Postgraduate Studies, The Medical College of Virginia, 1949-56.

Teaching Fellow in Histoanatomy, New York University, 1946-48; Military Service—U.S. Army Dental Corps, Chief of Dental Service, 39th General Hospital, 1942-46; Calhoun Scholar, Yale University Graduate School of Medicine, 1941-42; Carnegie Fellow, Yale University Graduate School of Medicine, 1939-41; University Fellow, University of Illinois Graduate School, 1938-39.

Association memberships: American Dental Association; American Medical Association; American Association for the Advancement of Science—fellow; American Public Health Association—fellow; American Board of Oral Medicine—diplomate; American College of Dentists—regent, 1968-72; Federation Dentaire Internationale; International Association for Dental Research.

Special awards, citations, or publications: D. Sc., honorary, University of Buffalo, 1961; Public Health Service Meritorious Service Medal, 1965; D. Sc., honorary, University of Pennsylvania, 1967; D. Sc., honorary, Boston University, 1969; Public Health Service Distinguished Service Medal, 1972; D. Odont., honorary, University of Goteborg, Sweden, 1973. Author of some 50 publications.

Mr. FLOOD. Do you have some people you want us to meet?

Dr. KRESHOVER. With me is Dr. DeWitt Stetten, Deputy Director for Science, National Institutes of Health; Dr. Ronald Lamont-Havers, Acting Director; Dr. Clair L. Gardner, Associate Director, extramural programs; John P. Patterson, Executive Officer, National Institute of Dental Research; Mrs. Frances H. Pettinato, Financial Manager, National Institute of Dental Research; B. F. Gardner, Jr., Chief, Budget Presentation and Coordination Branch, Division of Financial Management, and Charles Miller, Deputy Assistant Secretary, Comptroller.

Mr. FLOOD. Do you have a statement?

Dr. KRESHOVER. Yes, sir.

I would be pleased to read the opening statement, Mr. Chairman.

Mr. FLOOD. Fine.

Dr. KRESHOVER. Mr. Chairman and members of the committee, I am happy to appear before you again this year to testify for the National Institute of Dental Research.

The oral-facial area, which is the concern of this Institute, is subject to an incredibly large range of afflictions. These include the virtually universal problems of tooth decay and periodontal, or gum, disease; common ulcers which annoy or torment, and the less frequent but dread oral cancers; problems of malocculsion which affect an estimated one-third of the school children in this country; and the less common but severely disfiguring clefts and other craniofacial anomalies.

As you know, dental problems can cause excruciating pain. You may have read recently that a study in West German schools showed a positive correlation between bad teeth and bad grades. Surely, the pain associated with dental neglect must be reckoned as a factor in school performance everywhere. There are also profound psychological effects both on children and adults because the oral-facial region is so visible and has a role in many vital functions, including communication.

DENTAL CARIES

Our National Caries Program continues to pursue all leads to increase the resistance of teeth to decay, to modify caries-producing diets high in sugar and other carbohydrates, and to combat the effects of harmful bacteria involved in the caries process.

Water fluoridation, of course, is still the best means of decreasing the susceptibility of teeth to caries attack with its characteristic demineralization by acids in the mouth. However, for those communities that do not have the benefit of water fluoridation, other ways of providing the protection of fluoride are needed.

Recent research with animals shows that the greatest protection against decay comes from frequent exposure to low levels of fluoride dissolved in the mouth rather than from systemic incorporation of high levels of fluoride into the teeth. Therefore, during the year, we initiated a project to develop a method of prolonged release of fluoride in the mouth.

Research was also continued on several promising new fluoride compounds, notably the amine fluorides, ammonium fluoride, and titanium tetrafluoride which may have some value as mouthwashes.

During the year, we increased the support of community demonstrations of combinations of established preventive techniques. In particular, we want to relate the effectiveness of such projects to their cost in time, materials, and personnel. We have also designed these studies to learn how to motivate children to improve their dental health. In one approach, we are trying to get parents to involve themselves more in supervising their children's oral hygiene. We are also attempting to relate certain values expressed by students to the objectives of oral health programs, and to encourage student groups to compete in reducing plaque scores (measurement of bacterial film on teeth).

Encouraging results from experiments with both rodents and primates have led us to expand feasibility studies of a caries vaccine. Let me be quick to point out, however, that we cannot yet talk of testing a vaccine in man. It is necessary, first, to prove that a vaccine against only one organism will decrease decay significantly and, second, of course, that it is safe.

Meanwhile, we are supporting intensive investigations to determine which parts of various oral bacteria and which of their enzymes are likely to induce the most effective salivary antibodies. Also under active study are the ability of secretory antibodies in saliva to prevent bacteria from attaching to teeth; the levels of these substances in the film of dental plaque on teeth; and the feasibility of giving an immunizing vaccine locally in the ducts of the largest salivary glands, rather than as an injection under the skin.

PERIODONTAL DISEASE

In the complex area of periodontal disease, important biological information continues to be generated. Evidence is mounting that many microbes have the potential ability to initiate the disease. Moreover, the final loss of connective tissue and bone could result from a variety of inflammatory reactions of the immune system.

We now know that, in addition to the more familiar humoral immune reactions, in which antibodies and complement in the bloodstream defend against foreign substances, viruses, and bacteria, there are a host of cellular immune reactions.

Studies of chronically inflamed tissues indicate that when certain white cells become sensitized to bacterial and other foreign products, they produce chemicals which act in different ways. Some of these chemicals slow production of new proteins which cells need; some increase production of the enzyme collagenase, which degrades bone and tissue; while others exert further harmful effects.

In addition, studies on bone are producing better understanding of the specific bacteria, the particular cellular activities, and the precise biochemical substances associated with the localized destruction of the bone which supports the teeth. These studies have shown that the production of one bone resorbing factor requires the cooperation of two types of white cells. It was also found that humoral immunity mechanisms can increase bone loss by increasing the amount of prostaglandin, a potent bone-destroying hormone-like substance.

In recent human studies of a severe form of periodontal disease in which there is little inflammation of the gums, specific bacteria were found in areas of bone destruction. When transferred to animals, these organisms again caused bone disintegration with little or no inflammatory reaction. Thus, we now suspect that underreactions of the immune system, as well as overreactions associated with inflammation, can destroy bone.

In research designed to prevent periodontal disease, the efficacy of certain antimicrobial agents in controlling plaque was tested. The antibiotic kanamycin was promising. It protected handicapped children from gingivitis for nearly a year. Three daily applications given at 5-week intervals proved effective for 40 weeks. Actinobolin, another antibiotic with properties favorable for oral use, inhibited periodontal disease in rats.

PROTECTIVE FUNCTION OF SALIVA

Earlier research has shown that a very important factor in infection is the ability of harmful bacteria to bind to the cells of the tissue they infect. Newer findings reveal that mucins in the saliva can prevent the adherence of specific bacteria to epithelial cells which line the mouth. These mucins, large molecules of linked carbohydrate and protein, contain specific chemical binding sites just like those on the surfaces of the epithelial cells. Thus, many bacteria stick to molecules in the saliva and are washed away instead of adhering to and infecting the lining of the mouth. The salivary glycoproteins can also detach some bacteria from cells to which they have already attached.

HERPETIC INFECTIONS

Of considerable significance is the recent demonstration that the herpes simplex virus (HSV) can be isolated from the sensory ganglia of the nervous system of mice months after the acute infection of the lips, cornea, skin, or vagina has subsided. Injury to a nerve can reactivate this virus. These experiments in mice provide a model for studying the different kinds of herpetic infections in humans, including the oral (fever blister) and genital lesions produced by herpes type 1 and type 2, respectively.

Work is also under way to study the feasibility of developing a vaccine against herpetic infections. Preliminary tests show that immunization protected a large percentage of mice against developing a persistent infection with the oral strain of herpes, but did not protect mice against developing a persistent infection with the genital strain of herpes.

I might add another note. That is that the leading site for this area of research in herpes virus infection is very definitely within the National Institute of Dental Research. I think it has produced very significant findings, to date, of meaning not only in terms of oral and dental disease but other diseases as well.

CRANIOFACIAL ANOMALIES

Significant advances in the handling and treatment of children with cleft lip and palate include deferring the repair of a severe double

cleft of the lip until the upper jaw has been expanded orthodontically and all its parts lined up and stabilized. These studies show that it is possible to reduce the average number of operations by half without compromising the patient's welfare.

Embryologic studies to determine why the cleft palate fails to fuse properly continue to contribute new insights. Research with mice suggests that the tongue can interfere with palatal closure. In the young embryo, the tongue fills the space between the two sides of the palate. Earlier studies indicated that muscular movements of the growing embryo are the most probable cause of normal tongue displacement and that such movements are greatly reduced when the pregnant mouse is injected with cortisone, thereby explaining in great part why cortisone in the experimental model system does cause cleft palate in almost 100 percent of the studies conducted.

Since this hormone is secreted copiously during stress, these injections mimic some of the physiological effects of severe maternal stress on the mouse offspring. Thus, cortisone appears to depress the activity of the neuromuscular system in the mouse embryo.

As part of continuing studies of hereditary clefting, it was found that the incidence of cleft palate or cleft lip and palate in a group of Indians in North Carolina was 1 in 56 births, at least 10 times higher than the U.S. average. Analysis of family charts of all cleft individuals in this population showed that each of them was related to one woman who was born in 1832. While it is accepted that familial cleft palate is usually due to interactions of several genes, data from this study indicate that a major dominant gene accounts for certain types of cleft lip and palate.

You might recall, Mr. Chairman, that you asked me in previous years why we distinguished between cleft lip with or without cleft palate and cleft palate alone. Now we know they are two separate and distinct congential anomolies.

RESTORATIVE MATERIALS

Work that we are supporting at the National Bureau of Standards has progressed toward a standardized laboratory procedure for measurging the wearability of restorative materials. We expect that this research will enable scientists to determine how new materials will withstand use without resorting to long-term. expensive clinical testing. Preliminary results indicate that these laboratory tests do correlate with clinical findings.

We are currently funding a number of studies on tooth implants. Several designs fabricated from different materials, such as plastics, metals, and ceramics, are being tested in primates, dogs, and swine. So far we are encouraged to find that implants of titanium and some metal allovs designed with pores in the root-like portion have served successfully for 3 years in animals.

NUTRITION AND ORAL HEALTH

Nutritional studies of the past year have dealt primarily with protein deficiency and mineral metabolism. For example, scientists confirmed earlier animal studies indicating that protein deprivation

limited to pregnancy and the nursing period stunted growth permanently and also increased susceptibility to tooth decay in later life. The investigators believe that there is a relationship between nutrition, saliva, and decay since the volume and the protein concentration of the saliva of malnourished animals were several times less than that of normally fed animals.

One clinical finding during the year is that adults may need as much daily calcium as children. When the diet contains too little calcium, the body removes that element from the bones to maintain normal blood levels. Metabolic studies show that a level of 1,200 milligrams of calcium per day (the amount in a balanced diet including three glasses of milk) is most desirable to maintain calcium balance.

ORAL PAIN CONTROL

Pain is a complex experience which includes sensory and emotional components. Improved evaluation of pain control agents requires the development of new methods of measuring these aspects of the pain experience. NIDR-supported research has documented the existence of specific electrical responses in the brain to electrical stimulation of the tooth pulp in man. Thus, we now have available for the first time an objective physiological measure of the sensory component of pain, research, incidentally again, that is being conducted in our intramural program under Dr. Dubner's direction.

DENTAL RESEARCH INSTITUTES (CENTERS)

As part of their outreach to the dental profession, the five dental research institutes and centers supported by NIDR have intensified collaborative activities and dissemination of information on their work. For example, the center at the University of Washington distributes a regular newsletter and is actively developing a joint research project on periodontal disease with dental faculty at the University of Oregon. The institute at the University of Michigan also distributes a newsletter, and the center at the University of North Carolina has begun periodic mailing of its investigators' abstracts to schools throughout the country. These activities, as well as comparable efforts at the centers at the Universities of Alabama and Pennsylvania, should promote use of the institutes and centers as resources for other dental institutions and communicate research findings more effectively among the profession at large.

BUDGET REQUEST

In conclusion, Mr. Chairman, the budget request for the National Institute of Dental Reserach for fiscal year 1976 is $43,536,000. I shall be pleased to try to answer any questions and supply additional information desired for the record.

BUDGET REDUCTIONS

Mr. Flood. Well, that is a very interesting, impressive statement, as usual. However, the budget before us calls for a reduction of $6,297,000, from the 1975 fiscal year level.

Dr. KRESHOVER. Yes, sir.

Mr. FLOOD. Well, now, can you explain the impact of the reduction on all of the ongoing research operations of your institute?

Dr. KRESHOVER. I will try to address myself realistically to this question by commenting that the reduction in 1976, in view of the removal of the rescission figure for the current fiscal year, will quite obviously have impact on the opportunity to continue to support our so-called "noncompeting" continuation grants.

Those are the type 5 research grants. It is our estimate, therefore, that the amount of some $5,922,000 would be required to support 94 grants in this category that we could not ordinarily fund as a consequence of the fiscal 1976 budget. I say this not in connection with a plea for an increased budget, but rather to declare that a realinement and some reordering of our priorities will be necessary, Mr. Flood. These will be accomplished, I would hope, by quite obviously supporting fewer new starts but at the same time, perhaps, in accordance with Dr. Lamont-Havers and other expressions of programing issues at NIH across the board, apply some negotiated reduction of type 5 grants so that we would be able to support new applicants and new people.

Mr. FLOOD. We haven't been able to do anything about the chronic infection of realining priorities; have we?

All right, how many new grants are you going to be able to award under this budget?

Dr. KRESHOVER. Fifty-one.

They are distributed in the amount for fiscal 1976 of $2,659,000. This is our projection for 1976.

Mr. FLOOD. Take a look at page 125 of your justifications there. There you show a program decrease, $9,643,000. That is for your research grants. How much of that reduction relates to grant converting over to a competing status?

How much of that is simply due to not meeting your prior commitments?

Dr. KRESHOVER. In 1975, Mr. Chairman, we have projected a support in competing projects that are type 1 and type 2's, of 156 in the amount of $8,301,000. Quite obviously those competing projects would become noncompeting in 1976. Noncompeting grants in the amount of $3,721,000 will convert to competing grants. The balance of $5,922,000 would be type 5's which could not be supported unless all type 5's are negotiated.

CONTRACTS

Mr. FLOOD. Your budget also shows another reduction of $566,000. That is in your research contract commitments. What is the impact of that reduction?

Dr. KRESHOVER. Again, I would suggest that we will have to negotiate appropriate reductions in support of our contracts. At the present time we are projecting for fiscal 1976 some 57 contracts in the amount of just slightly over $41½ million. These are distributed, as you would expect, with the greatest emphasis on our national caries program. Accordingly, if priorities again are to be exercised realistically, it is my intention that we should provide continuing support in a reason-

ably continuing strong fashion to this program. As you know, it is largely applied in nature. Development and applied research, if you will.

There are other categories we might very well find ourselves having to negotiate downward in order to realize certain objectives in our contract program.

SUPPORT BY FEDERAL AGENCIES AND COLLABORATIONS

Mr. FLOOD. By the way, how much money is used by all these other Federal agencies such as the Department of Defense, and I happen to have been on the Appropriation Committee for the Department of Defense ever since it was created. Over at the VA, for instance, there is quite an operation. What do they spend on dental research?

Dr. KRESHOVER. Well, I was not too prepared, but my executive officer, Mr. Patterson, was and he provided me with this backup and I do have it.

Mr. FLOOD. That often happens.

Dr. KRESHOVER. The total Federal support in 1973—and we have complete figures for that year—was in the range of $52⅓ million.

I am referring now only to Federal support. Of this aggregate amount the National Institute of Dental Research provided 66 percent of the support.

The DOD provided 9 percent; VA, 2 percent; other components of the Public Health Service, 21 percent; and other components not identified, about 2 percent.

Mr. FLOOD. How do you coordinate your research with all these other Federal agencies?

There is a Navy outfit, they have quite a dental research institute.

Dr. KRESHOVER. While I would like to be able to say that formal mechanisms are established, I believe that the most effective collaborations and communications that the Institute has with these other agencies have been scientist to scientist and science administrator to science administrator. I think we have enjoyed a profitable exchange with these other organizations. We have also published a document, "Dental Research in the United States, Canada and Great Britain," that states clearly all categories of research for everyone to see.

Mr. FLOOD. I have seen that in three different colors.

Dr. KRESHOVER. That represents each year so it is updated. We are proud of that.

In addition to these kinds of investigator-to-investigator collaborations, we have had close working communications with the VA through their participation on the National Advisory Council affairs as well as representation by the DOD.

DIABETES

Mr. FLOOD. There has been a lot of action and interested concern and properly so, and these things happen in sequence, about diabetes. People tell us that destruction of the bone and gum is not unknown with the whole general population. They tell me that destruction of bone and gum virtually affects the entire 10 million people of the population afflicted with diabetes. You know about the Diabetes Act. That

requires your Institute, specifically requires your Institute and, of course, all the other Institutes at NIH, not just you, to devote part of your budget to diabetes research.

What are you doing in that area?

Dr. KRESHOVER. We are proud of a very small effort. Needless to say it is small, being in a dental institute. But your observations are quite accurate.

Mr. FLOOD. That is why I made them.

Dr. KRESHOVER. Well, I think they are accurate in the sense that we recognize a relationship.

We don't know the extent of it. We do know, for example, that in diabetes mellitus there is an involvement of the vascular system and, by and large, this manifests itself in the oral tissues. So the relationship of periodontal disease to diabetes is quite obvious. There has been some experimental work in the laboratory that I had some part in in the past. That had to do with the production of experimental diabetes with the drug alloxan to show the relationship of the experimentally induced disease to the oral tissues.

The scientist who represents the Institute on the coordinating committee of the National Commission on Diabetes has, in the course of his own research, made some extremely interesting contributions with respect to a virus as related to diabetes.

Again, this work was done in the experimental animal model system. As far as how much money we put into diabetes research in our programs, I would have to put that in the record. We can price this out by examining the laboratory activities.

Mr. FLOOD. Fine.

We are asking all of the institutes about this.

[The information follows:]

The NIDR is interested in diseases which are more or less specific to the oral cavity and to systemic diseases which have manifestations in the oral cavity. The Institute is interested in diabetes primarily in terms of its effect on the oral cavity. Diabetes is clearly not one of the Institute's major areas of emphasis, but this disease is of interest to several of the major disease programs of the Institute.

The following is a list of diabetes-related activities supported by NIDR:

Project No.	Investigator	Subject heading	1975
P13DE02623(16)	Rosenbloom, J.	Pancreas hormones, insulin	$165,000
P13DE02668(57)	Hanker, J. J.	Neuropathy, diabetic mice	45,000
R01DE03022	Gangarosa, L. P.	Microcirculation, diabetes	53,048
R23DE03277	Anapolle, S. E.	Metabolic disorders (inborn)	22,170
R01DE03764	Brightman, V. J.	Metabolic disorders (inborn)	69,235
74B-111 (NIDR)	Ross, M. E.	Diabetes mellitus, pancreatic diseases	140,000

PERIODONTAL DISEASE

Mr. FLOOD. Now, with regard to the periodontal disease, we see the same statement in your justification material this year that we saw last year.

Treatment of periodontal disease is time-consuming, costly, frequently unsuccessful, and it remains essentially unavailable to the majority of the population.

That is what you said. Don't you have anything positive or new to report in that area at all?

Dr. KRESHOVER. I sure do. I think again the important thing that I would relate to you and this subcommittee is the fact that the state of the art, the advancement of knowledge in the area of periodontal disease has been slow in coming. It is a complex disease as you well have recognized. At the same time, some of the activities in the course of the last year that have been conducted in our intramural Laboratory of Microbiology and Immunology have been highly significant. We now know far more about the causes, mechanisms of action, and patterns of disease progression in periodontal disorders than we did before. We know periodontal disease is an expression of the immune response of the body to the infectious process. We have departed from the old understanding that periodontal disease can be easily explained by examination of its microbiology. Rather, we are now examining the immune response of the body which, in its attempt to succeed in overcoming an infection, actually produces a deleterious or injurious effect.

Mr. FLOOD. That does not surprise you. The body always has. There is not anything new about that.

Dr. KRESHOVER. We have not always been able to say "hey, now we have made very significant advances." I think this is a demonstration of where there has been considerable impatience on the part of many, excluding knowledgeable lay groups and, quite obviously, the knowledgeable scientific and health profession groups; an impatience to get on with application without having the necessary reservoir of new knowledge and new information to apply. In this particular instance I do think that the periodontal disease problem is being faced, expediently, with approaches to control infection with rather inadequate knowledge but that it may very well be in the course of the next half a dozen years that the body of scientific knowledge will be sufficient to really do things in the periodontal disease area that we are currently doing in our national caries program.

Mr. FLOOD. I am certainly glad I asked you that question.

Dr. KRESHOVER. I am, too.

CARIES PROGRAM

Mr. FLOOD. In 1971, you were talking about the start of the caries program. What about summarizing your activities to date on this program? What are you going to do in the coming year?

Dr. KRESHOVER. The emphasis began in 1971. At that time, as you recall, your subcommittee and the counterpart subcommittee in the Senate, provided us with the add-on dollars with which to accelerate and provide support for a concerted program.

Mr. FLOOD. You made a good presentation.

Dr. KRESHOVER. We thank you for the support. It was based, quite obviously, on the fact that we did recognize that an adequate body of knowledge was available with which to move forward and bring it to public utility.

At the present time, Mr. Chairman, we are emphasizing what we call, in NIH and Government health parlance, I suppose, demonstration and control programs in our national caries effort. So that we do believe that there are sufficient measures available today to make an impact. To cite two examples, we are now testing a mouth rinse constituted of fluoride in certain chemical formulations. We are also

demonstrating fluoride administration in the form of a tablet, with particular applicability to communities where fluoridated water is not available to the population. In these programs, we are trying to attract participation through contract support.

FLUORIDATION

Mr. FLOOD. Is there much of this organized local community effort against fluoridation?

I have not heard much about that lately. Four or five years ago it was a big deal with parades and banners.

Dr. KRESHOVER. I share your observation. Hopefully, for reasons that will persist, this opposition has declined.

I believe that today we are on the threshold, through our programs in the national caries effort, of demonstrating both to the professional community, to the children of the country, and, even more importantly to their parents, that it is possible in programs conducted in our public school systems, for example, to do much to reduce dental caries and control its level of prevalence and severity.

Mr. FLOOD. Again, in your justification—you know we read these justifications——

Dr. KRESHOVER. I can see that.

PUBLIC EDUCATION

Mr. FLOOD. You say caries control through decreased consumption is made difficult because of the public predisposition for sweet foods. What are you doing to make people aware of this problem?

Dr. KRESHOVER. Not to beat the drum unnecessarily loud on behalf of our Office of Scientific and Health Reports in the Institute, there has been a magnificent contribution in the dissemination of this kind of information, not only to the professional community, but to the public. We have recognized, for example, that the ingestion of sucrose, table sugar, on a continuing repetitive basis in snacks throughout the course of the day is extremely deleterious.

Mr. FLOOD. Are you fellows responsible for the moving of sugar bowls out of the restaurants or did price have something to do with that?

Dr. KRESHOVER. The economy has had a great impact on that. But you recall in last year's discussion, Mr. Flood, the point came up that some of the Scandinavian countries actually substituted for sucrose, in their confectionaries, other kinds of carbohydrates, with some success. But this is a problem quite obviously of public communication, information and education.

Mr. FLOOD. Do I understand from you that you are out promoting sugar-free diets? A lot of people are. What about you?

Dr. KRESHOVER. I think it would be fair to say that the activities of the NIDR, and it would be presumptuous of me to relate this across the board to other Institutes—the activities of the NIDR, with an understandably limited budget, have necessarily been in the conduct and the pursuit of scientific endeavors both in our intramural activities and our extramurally supported programs. This has left very little time and resources to engage in a public information campaign that I

believe is handled eminently well by some of the organized health professional groups, as, for example, the American Dental Association and other like specialty associations that represent the practicing community and how it relates to the using public; that is, its patient clientele.

SEALANTS

Mr. FLOOD. You seem to have a pretty good record, on memory at least, of the things we talked about last year.

Last year you remember we talked for some length about tooth sealants. There was a series of incidents and we brought it up about tooth sealants. I think I got you off balance because you said pretty glibly right away, well, all the answers are not in yet. Well, that was last year. You said you were now just about completing your second year and you were in there punching and this is going to be a 3-year study. You were finishing the second year and you were all in there on the thing. OK, here we are. This is the third year. What do you have to report now on the subject? You are at the end of the third year.

Dr. KRESHOVER. It is quite timely to comment on this, then.

Mr. FLOOD. That is why I asked you.

Dr. KRESHOVER. We continue to have the evidence that the sealant applied appropriately on the so-called occlusal surfaces of the posterior teeth has been effective, following a single application, for a time period approaching 3 years, and that the percentage of reduction of caries has ranged all the way from some 60 to 65 percent to 99 percent. These are very significant findings, quite obviously.

I believe that we are now at the point again—and this is not to be evasive—as I indicated in connection with the mouth rinses of fluoride and the tablet, of demonstration programs to prove the utility of the sealant in the population at large.

I think one of the very critical issues relates to the manpower problem. Who will be available and properly trained to provide the sealant in the magnitude of treatment need?

Mr. FLOOD. For the purpose of the record, what are we talking about when we say "sealant?" What is a sealant?

Dr. KRESHOVER. A sealant is a resin, a methacrylate resin not unlike a plastic, that is in liquid form.

Mr. FLOOD. Somebody has to ask these questions.

Dr. KRESHOVER. Of course.

It is painted on the teeth. Then there are various ways of "curing" or "hardening" this liquid resin. In the case of the methacrylate preparation, they use an ultraviolet light that is directed onto the tooth surface and it hardens the resin.

Mr. FLOOD. Does it cost a lot of money?

Dr. KRESHOVER. It is most inexpensive. The problem we have facing us is how to deliver a proven therapeutic measure.

Mr. FLOOD. When is this going to become routine?

You are at the end of the third year now. When is this going to become a routine procedure with the dentists?

Dr. KRESHOVER. There are many dentists using this today. The problem that this subcommittee obviously needs no reminding about is that only some 45 to 50 percent of our total population in this country

either seek or have dental care available to them. That 45 or 50 percent present no problem. It is the 50 to 55 percent with an inadequate number of health professionals and allied personnel to deliver a therapeutic product that presents a problem. It seems to us in the dental profession that we have to examine, through these demonstration projects, the expertise with which a less than professionally trained person can properly deliver this kind of therapeutic application.

Mr. FLOOD. There is no reason why a paramedic cannot do this, is there? It is no big deal.

Dr. KRESHOVER. There are many issues, quite obviously, in terms of ancillary or paramedical personnel delivering care. There is a matter of skill, the complexity of what is involved, the safety of the patient in terms of educational factors.

Mr. FLOOD. That is true anytime a paramedic does anything, all those conditions are precedent.

Dr. KRESHOVER. In dentistry this is a subject of paramount importance that you have yourself explored many times in the past in your addresses to various dental associations.

There is no quick and ready answer, as you have pointed out yourself.

PAIN CONTROL

Mr. FLOOD. On page 145 you said you are exploring the potential of acupuncture for dental pain control. All right, specifically what are you supporting? You say you are supporting something in this area.

Dr. KRESHOVER. I would say at the outset that the interest of the National Institute of Dental Research in acupuncture, so-called, is part and parcel of a broader expression of interest at the National Institutes of Health across the board. We share this interest with other Institutes, including the NIAMDD, the NINCDS, the NIGMS, and the like. We also happen to have in our intramural program, a neurophysiologist, Dr. Dubner, with a dental background and a Ph. D., who has been a significant contributor to our understanding of pain. He participated in the visit to the People's Republic of China in this past year with an expert team to observe acupuncture. We also are supporting one study at the Massachusetts General Hospital concerned with acupuncture. That is of rather recent origin.

We have acquired some considerable knowledge about the presumed mechanisms of acupuncture that has not been an outcome of our own Institute's research but rather has been a contribution by many scientists. There are several people we have worked very closely with as consultants, including Dr. Bonica, Dr. Papper, and Drs. Melzac and Wall; the latter two having evolved a theory that, in their judgment, explains how and why acupuncture might work.

We believe that the evidence is in hand that warrants a continued scrutiny of this problem. We are participating with the NIH in a small way to try to add to this base of knowledge.

Mr. FLOOD. Mr. Patten?

ORAL CANCER

Mr. PATTEN. Since we have a medical school now at Rutgers, I have a new interest in your work. It is outside of your line, but two of my letters this morning asked for help to get people into dental schools.

You talked about the $607 million for cancer. Ten years ago I heard a cancer specialist at the Memorial Hospital in New York just bemoan the fact that this patient had been treated by a dentist for a year and the dentist didn't recognize his mouth was loaded with cancer. Wouldn't you say the dentists you have could recognize cancer in the early stages; or is that hard?

Dr. KRESHOVER. I would suggest that that is a very unusual and isolated circumstance. The National Cancer Institute has for many many years now been supporting in all of our dental schools, programs in cancer detection, programs in understanding of the recognition of cancer in the oral environment. It is so frequently the dentist who is the first person to recognize oral cancer. I would suggest that it is the reason, also, why oral cancer, which constitutes some 4 percent of all cancer afflicting man, and most notably lip cancer, which is the most common type, is the most successfully treated from the standpoint of 5-year cures.

It is because of early detection that this is possible.

RESTORATIVE MATERIALS

Mr. PATTEN. When I was 28 years old, I sat with five people in city hall. They were all young. I was the only one who had my teeth. All the rest had dentures or partial dentures. This surprised me. Are dentures part of your research work?

Dr. KRESHOVER. Yes.

Mr. PATTEN. There are problems and there is work for you?

Dr. KRESHOVER. Yes, very definitely.

Mr. PATTEN. That is all new to me.

It just occurs to me that you sat here and for the millions who are using partial dentures or dentures I didn't know whether there was something in your line of dental research.

Dr. KRESHOVER. Yes, sir. In the new structure the National Institutes of Health has devised for the presentation of their budget justifications, they are listed according to program areas. One of the principal six areas of the National Institute of Dental Research is called "restorative materials." We are very interested in that and it is extremely important.

RESEARCH CAREER AWARDS

Mr. PATTEN. I notice the cut in your research career programs from 33 awards in 1975 to about 28 awards in 1976. Is this in line with the general budget problems or is there some other reason?

Dr. KRESHOVER. Would it be improper if I were to refer this to Dr. Gardner?

Mr. FLOOD. No. He can sound off anytime he wants.

Mr. PATTEN. Is it that we don't need it, or is it a budgetary item?

Dr. GARDNER. I would say we do need it, but one has to make choices when you have a certain amount of money.

Mr. PATTEN. Could we have a list for the record of the awards in 1975 and those who are continued in 1976?

Dr. KRESHOVER. Yes, by all means.

Mr. PATTEN. I like to know what is happening around my area.

[The information follows:]

RESEARCH CAREER AWARDS

Name	University	Total
Schachtele, Charles F	University of Minnesota	20, 837
Taubman, Martin A	Forsyth Dental Center	22, 500
Eisenberg, Roselyn J	University of Pennsylvania	22, 918
Emmings, Fred G	SUNY at Buffalo	23, 562
Taubman, Martin A	Forsyth Dental Center	23, 500
Baylink, David J	University of Washington	24, 500
Shaw, James H	Harvard University	30, 780
Goepp, Robert A	University of Chicago	25, 000
Lazda, Velta A	American Dental Association	17, 640
Hock, Janet M	University of Iowa	23, 500
Cohen, Michael M., Jr	University of Washington	19, 680
Bekhor, Isaac	University of Southern California	24, 200
Steffek, Anthony J	American Dental Association	24, 250
Young, Franklin A., Jr	Medical University of South Carolina	24, 570
Schnitman, Paul A	Harvard University	21, 000
Schneyer, Leon H	University of Alabama in Birmingham	32, 256
Simmons, Norman S	University of California, Los Angeles	31, 050
Redman, Robert S	University of Minnesota	18, 290
Boskey, Adele L	Hospital for Special Surgery	18, 000
Price, Steven	Virginia Commonwealth University	22, 500
Mooser, Gregory	University of Southern California	23, 500
Dreyer, Duane A	University of North Carolina Chapel Hill	16, 640

Note: 5 additional research career awards will be awarded in fiscal year 1975.

Mr. PATTEN. Will some new awards be made in 1976?

Dr. KRESHOVER. No, not in that area.

Mr. PATTEN. Do you think the American people have a fair appreciation of your efforts in dental research?

Dr. KRESHOVER. Yes, I do.

You mentioned Rutgers before. To your knowledge are they planning a school of dentistry? They were at one time when Dr. Stetten went there some years ago.

Mr. PATTEN. You know, Dr. Stetten was the first president of the medical school. At that time it was medical and dental.

Dr. KRESHOVER. Dr. Stetten had been extremely interested in starting a dental school when he went there as dean some years ago.

Mr. FLOOD. Mr. Natcher.

TOOTH IMPLANTS

Mr. NATCHER. Doctor, are you still working on the tooth implantation program?

Dr. KRESHOVER. Yes, sir, we are.

Mr. NATCHER. What are you doing, Doctor?

Dr. KRESHOVER. At the present time the tooth implantation program is concerned primarily with an investigation of the most promising of the implant materials that we have been able to identify: the so-called calcium aluminate. The advantage of this over metals and many of the plastic and ceramics that have been tried in the past is several fold.

In the first instance, the calcium aluminate can be prepared in a fashion to control the size of the pores, the very minute channels in the peg that is introduced into the bone, the so-called endosseous

implant. It has been demonstrated in recent research that if these pores are of the size of 100 to 200 microns, then new bone can infiltrate the pore system of the implanted synthetically prepared tooth and create great stability. These researches have been done in the subhuman primate, the baboon. Now, I believe, the retention period is in the range of some 3 years.

The other thing demonstrated by the calcium aluminate, and needless to say we are concerned about all these products, is that it is neither toxic nor carcinogenic; it is inert. It is also subject to a wide variety of shaping maneuvers, and it has great stability. So our implant research continues to move vigorously forward. We have only one concern. I have hesitated to note it for the record, although it was mentioned last year in response to some of Mr. Flood's questions: That is, to what degree of utility is this being put today in dental practice? The answer is considerable. At the same time, we at the National Institute of Dental Research, and our colleagues on the Council of Research of the American Dental Association, are rather concerned that, one, there not be premature utilization across the board of implant techniques without an adequate base of scientific knowledge, and, two, that the operative or surgical procedure to place these implants does in fact require more than a one-half day continuation course experience in a dental office of a practitioner who might have done it with some skill himself. So we have, with the American Dental Association, gone on record as being extremely concerned about its premature utility in practice and that it still warrants categorization as an experimental approach to tooth replacement. We do not yet know enough about the implant to put it to wide use.

DENTAL MATERIALS

Mr. NATCHER. Is there any change from your appearance last year concerning the materials now in use to take the place of gold from the standpoint of crowns and other dental work?

Dr. KRESHOVER. There are two areas, I believe, that I did not call attention to last year because they were rather new. There has been a recent development of some considerable significance. I refer to an alloy constituted of cobalt, chromium, and nickel in certain proportions, which, by the addition of tantalum rather than the traditional use of carbides, becomes an alloy having a greater degree of strength and a greater degree of so-called ductility. So it has great promise. Another contribution in the materials field is a new composition of amalgam. An amalgam, incidentally, is nothing more than two metals, one of which is mercury, brought into combination.

The traditional kinds of amalgam alloys have been constituted of mercury, tin, and silver. Our researches through grant support have found that the addition of gold gives it greater strength and, more importantly, less corrosiveness, so that the amalgam will not corrode as is so often found to be the case where it is in mouths for a period of years.

Mr. NATCHER. Thank you very much, Doctor.

Mr. FLOOD. Mr. Michel.

MANPOWER

Mr. MICHEL. Doctor, do we have enough dentists in this country at the present time?

Dr. KRESHOVER. My response would be no, although you would find health professionals who would suggest that the greater concern is with geographic distribution. I had entered into the record last year, and I won't bore you with a repetition, the projected need for dentists by 1980.

Mr. MICHEL. That indicated a shortage of 50,000 by that year, has that changed?

Dr. KRESHOVER. No; except that our production of dentists, and especially auxiliaries, has already increased significantly. Accordingly, our earlier figure may have to be revised downward. The range of predictions is great depending upon what assumptions are made regarding the economic situation, birth rate, and dentist production.

Mr. MICHEL. How many dental schools are there?

Dr. KRESHOVER. Fifty-nine; three more than last year.

Mr. MICHEL. The three additional are where?

Dr. KRESHOVER. One in Mississippi, one in Colorado, and the other in Stony Brook, N.Y.

FEDERAL SUPPORT

Mr. MICHEL. How many of these 59 schools receive any grant or assistance from the National Dental——

Dr. KRESHOVER. There is probably not a single dental school that does not, or has not recently, received some support from the NIDR. I, of course, am not counting new schools.

Mr. MICHEL. I do not want to be untruthful, I would assume so and if in checking you can corroborate that for the record.

Dr. KRESHOVER. I will.

Mr. MILLER. You recognize the capitation support comes from the health resources administration.

Mr. MICHEL. Right, but I also wanted a specific answer in the area of grant or assist from the National Institute of Dental Research.

What percentage of the extramural grants which you award actually go to dental schools?

Dr. KRESHOVER. Again, I will be in the ballpark, Mr. Michel, but not with great accuracy. Approximately 50 percent of our research grants apportionment in our appropriation will go to schools of dentistry, the rest will go to schools of medicine, research institutes, and the like. This is a fine figure to relate because, in our judgment, it connotes an emphasis on the quality of support for research in dental disease regardless of professional discipline or health field affiliation.

Mr. MICHEL. If that other 50 percent were going to medical schools, would that tend to be those medical schools at the same location where there is a dental school?

Dr. KRESHOVER. Most likely this will be the case.

Mr. MICHEL. One of our institutions of higher learning?

Dr. KRESHOVER. Right.

Mr. MICHEL. While we do have a limited number of facilities, is there a shortage in the number of individuals choosing dentistry today or inclined to go into dentistry?

Dr. KRESHOVER. I am embarrassed to say I do not have specific figures but applications to our schools of dentistry have increased by leaps and bounds in recent years. I know, for example, that one of the dental school deans who I spoke to recently indicated they were accepting something like one in eight applications. So this speaks well of the program and its attractiveness.

ECONOMICS

Mr. MICHEL. Do you have any estimates on how dentists fare compared to other medical professions from an economic standpoint? What is the average cost to produce one dentist, and how does this compare to other professions in medicine?

Dr. KRESHOVER. We do have some figures that are, in general, somewhat responsive. For example, a comparison made in 1972 of the mean net incomes for dentists and physicians showed the former at a level of over $34,000 and the latter at approximately $47,000. The figures for some subgroups, according to certain specialty areas, showed a rather comparable differential.

With regard to the cost of education per student by health profession, some recent figures cited by the Institute of Medicine of the National Academy of Sciences may be of interest to you which I will supply for the record.

[The information follows:]

Health profession	Average cost	Range
Medicine	$12,650	$6,900 to $18,650
Osteopathy	8,950	6,900 to 12,350
Dentistry	9,050	6,150 to 16,000
Optometry	4,250	3,750 to 4,750
Pharmacy	3,550	1,600 to 4,950
Podiatry	5,750	4,400 to 6,700
Veterinary medicine	7,500	6,050 to 10,500

CANCER RESEARCH

Mr. MICHEL. You refer to the work being done at the National Cancer Institute as directly relating to some of the same areas of interest. Are any of the other Institutes doing work along any of these areas?

Dr. KRESHOVER. As you, of course, know, Mr. Michel, the National Cancer Institute has the primary responsibility in this area. However, in parallel with our own Institute's special interest in oral cancer and such important precancerous lesions of the mouth as leukoplakia and submucous fibrosis, you are aware, I'm sure, of the attention given by other Institutes to cancers of special interest to them. I believe that an example might well be the interest of the NIAID in Burkitt's lymphoma, a tumor that involves the jaw.

RESEARCH GRANT APPLICATIONS

Mr. MICHEL. Could you provide, for the record, the number of research grant applications you receive in each of the areas of research

funded by the Dental Institute and the number that are actually funded in each?

Dr. KRESHOVER. Yes.

[The information follows:]

1974 RESEARCH GRANTS

Program area	Applications received	Awards funded
Caries	157	68
Periodontal and soft tissue diseases	162	103
Craniofacial anomalies	140	60
Restorative materials	71	32
Pain control and behavioral studies	25	9
Dental research institutes	5	5
Total, NIDR	564	282

DENTAL CARE AND PUBLIC EDUCATION

Mr. MICHEL. Do you have any figures showing the number of people who avail themselves of regular dental care? Do most people have a regular checkup once or twice a year as recommended?

Dr. KRESHOVER. This is a difficult question to answer, Mr. Michel, because our data are still purely tentative assessments. In general, however, we must recognize that there is a difference between availability of dental care and the degree to which the public avails itself of such care. There is, of course, the other aspect of the problem which is simply an inaccessability of some segments of the population to health care. A perhaps reasonable figure is that some 110 million Americans annually avail themselves of or seek dental services.

Mr. MICHEL. Have you been pursuing any new methods of public education in this area which show promise?

Dr. KRESHOVER. Yes, Mr. Michel. I would take this opportunity to call to your attention some of the activities of our Institute's Office of Scientific and Health Reports. Over the past year, it distributed in response to individual requests over 58,000 publications dealing with dental decay, periodontal disease, nutrition, dental health, and the related and obvious need to seek dental consultation and service. In addition, this office made a number of reports to the public via television and the news media. An especially important focus of attention has been the National Science Teachers Association and the National Association of Biology Teachers in view of the educational target; that is, the young student in primary and secondary school. I believe, Mr. Michel, that the contributions by the National Institute of Dental Research to these educational needs have been significant and are primarily made via our Office of Scientific and Health Reports, as just recounted, and the currently developing demonstration projects planned by our national caries program as I earlier reviewed them with Mr. Flood.

Mr. MICHEL. Have you completed any studies as to the effectiveness of education programs carried out through individual dentist's offices? Have we been able to develop an effective dental hygiene program that could be easily presented? In a recent discussion with a small group of people, there were a number of different approaches put forth by

some of my friends, based on their own personal experiences with their own dentists. The methods of education seemed to vary from personal lessons from the nurse to an automatic, short slide presentation which each patient was shown with each visit to the dentist. It was interesting to note that there was quite a difference in the recommendations of everything from how to brush teeth to what kind of toothbrush to use. Have you made any studies into these areas and have you made any recommendations?

Dr. KRESHOVER. I believe, Mr. Michel, that the contributions by the NIDR to these educational needs have been made in two areas—by the activities of the Scientific and Health Reports Office, as just recounted, and by the demonstration projects currently being developed by our national caries program which I mentioned to Mr. Flood.

Mr. MICHEL. Doctor, I commend you for what you are doing out at the Institute today and appreciate your response to the questions which I have asked.

Dr. KRESHOVER. Thank you so much.

Mr. MICHEL. On the record, if I might, I do not know whether or not I have heard right through the grapevine that this may be your last appearance before the committee, if it is I am sure it is of your own volition?

Dr. KRESHOVER. Yes, and 19 years of service at the NIH.

Mr. MICHEL. And very laudable service for which we commend you and thank you again for all you have done.

Mr. FLOOD. Mr. Conte.

CARIES INCIDENCE

Mr. CONTE. Dr. Kreshover, could you give us some statistics on the incidence of caries in the population? What portion of the population is affected, and what is the average number of caries per person?

Dr. KRESHOVER. One could cite a variety of statistics to document the unusually high incidence of dental caries in this country. For example, Mr. Conte, the average 15-year-old has as many as 11 decayed teeth, and the young child, upon reaching school age, has accumulated 3 decayed teeth. In all, therefore, we can note that dental caries is perhaps among the most prevalent of diseases, affecting 98 percent of our population.

Mr. CONTE. There are some lucky people who never get caries. Are some people just naturally resistant, or is it simply a matter of better dental hygiene? Have you done any work with people who don't get caries?

Dr. KRESHOVER. As your question implies, Mr. Conte, there are indeed those rare and unusual individuals who are spared from caries attack because of some presumed inherited factor. For many years, dating back to some experimental work at Michigan by Drs. Hunt and Hoppert, we have known that a caries-resistant strain of rat can be raised. More currently, the work of Dr. Rachel Larson in our own NIDR laboratories, has further demonstrated the genetic influence in experimental caries in animal model systems. With regard to humans, a longstanding project conducted by dental researchers with the Department of the Navy has demonstrated the hereditary resistance of caries among young Navy personnel. However, it is perhaps

fair to say that the genetic factor or factors represent a complex picture that is most difficult to sort out from other recognized environmental factors such as bacterial infection, diet, and state of oral hygiene. From this still incomplete story of caries etiology, we can only conclude that no single genetic factor has yet been recognized that would explain hereditary differences in caries susceptibility in humans.

FLUORIDATION

Mr. CONTE. There have been some recent reports of plans to fluoridate the water supply of every community in the country. Is this a practicable project, and would you support such an effort?

Dr. KRESHOVER. As you, of course, know, Mr. Conte, of the some 211 million people constituting our total population today, only about 165 million reside in communities served by public water systems. Among the latter group, only about 97½ million receive the benefit of fluoride added to the water in amounts to accomplish an adjustment to the optimum health level. Needless to say, it would be in the best interest of public health if all communities served by public water systems could be fluoridated. The estimated cost would not be unreasonable. In fact, some recent statistics have shown that if an appropriate Federal-local matching program could be developed, a ball park figure for national governmental cost over a 5-year period would be less than $30 million. The balancing benefits measured in terms of reduced costs for dental care would be so manyfold as to make the Federal investment most profitable. I should remind you, however, as well as call to the attention of the subcommittee, that by fluoridation we are merely solving only half of the caries problem in terms of disease control, and that caries is but one of several major health problems that affect the mouth and related structures. Accordingly, attention to program balance would argue strongly for comparable and continued attention to the still formidable problems of periodontal disease, acquired and congenital craniofacial deformities, oralfacial pain, and benign and malignant ulcerations, and other lesions of the mouth.

Mr. CONTE. You mentioned research on some of the new fluoride compounds. In what stage of research are you with these? Are these substances proven safe for human use yet? Have you done any clinical studies with them?

Dr. KRESHOVER. I had the opportunity just recently of getting some updated information on this question from Dr. Carlos, our Institute's Associate Director for the national caries program. By my recollection, he noted that in vitro testing of several new topical fluoride compounds showed a ready uptake by the tooth enamel of the fluoride compound, and a longer period of retention than had been earlier observed for the older preparations of sodium and stannous fluoride. These tests, incidentally, are now in clinical trial stages, and we will not expect any results before next September. Regarding the matter of safety, it should be noted that these fluoride compounds, as well as all other chemotherapeutic agents that we test in clinical trials, must conform to regulations of the Food and Drug Administration. Indeed, we do not ever initiate or support research on a drug unless it has been approved by the FDA for human experimentation. In the case of the

fluoride compounds I have been referring to, they can be regarded as entirely safe for human use.

DEMONSTRATION PROGRAMS

Mr. CONTE. Would you describe one of your community demonstration programs? What are the mechanics of such a program? How many of these do you have operating now, and at what cost per person served?

Dr. KRESHOVER. I will refer again, Mr. Conte, to the work described recently by our national caries program. In summary, we are now in the process of implementing a new community demonstration program in elementary school classrooms. This project is a deliberate attempt to show to the public and the dental practitioner, the advantage of widespread use of a caries-preventive method (that is, fluoride mouth rinse) which has been proven to be safe and effective in previous clinical research. According to plan, we expect to support some 20 projects by contract in carefully selected sites of the country to demonstrate cost, personnel requirements, and public acceptance of methods of caries prevention. A significant part of the plan calls for a commitment by the community to continue the program after termination of the Federal support for its demonstration. By present calculation, the cost per child per year for this project will be no more than 50 cents.

VACCINES

Mr. CONTE. When you talk about a caries vaccine, are you suggesting the possibility of immunizing people against the bacteria which cause caries? I understood that caries formation was largely a dental surface process, not affected by the immunological system of the body. Could you explain how a vaccine might work?

Dr. KRESHOVER. Research to assess the feasibility of developing a vaccine has notably increased in the past year. I would cite our own efforts at the NIDR as an extension of some earlier work done by Dr. Bowen while he was at the Royal College of Surgeons in London, and parallel investigations by Dr. Genco at the State University of New York at Buffalo on the subhuman primate.

While these studies are promising, it should be emphasized, as your question implied, that the development of an acquired immunity via vaccination would necessarily be different for caries than for other kinds of bacterial diseases where circulatory antibodies are effective. Quite obviously, the anatomical location of the teeth, and the susceptible sites for caries lesions to develop, are such that any immune factors would probably have to be mediated through the saliva rather than the blood serum. Thus, one experimental approach has been to inject killed bacteria vaccine preparations directly into the ducts of the salivary glands.

ORAL-FACIAL PAIN

Mr. CONTE. I was very interested in your mention of the development an objective physiological measure of the sensory component of pain. Where do you go from here? What areas look fruitful for the development of a more effective dental pain reliever?

Dr. KRESHOVER. As you know our activities in pain control, both intramural and extramural, have received considerable attention in the past few years. Indeed, the development of appropriate and useful model systems for pain measurement is a subject of high priority. At the present time our major target is to gain the essential fundamental knowledge by which the mechanisms of pain mediation and expression can be better understood. Paralleling this effort is our attention to the development of more effective drugs for alleviation of pain. Here, our efforts have been focused on such agents as Brevital and Diazepam.

OPERATIVE DENTISTRY

Mr. CONTE. Are you doing any work in the development of better dental treatment technology? I am speaking in terms of more effective drilling, cleaning, and filling procedures and equipment.

Dr. KRESHOVER. As I also indicated earlier, we are giving considerable attention to research in restorative materials. In addition to the development of newer products for practitioner use, I would also call your attention to the significant work of the Institute some years ago, conducted by Dr. Stanley, now at the University of Florida. These studies were, indeed, milestones in the assessment of drilling and related operative procedures as regards their influence on the dental pulp tissue.

DENTAL RESEARCH INSTITUTES/CENTERS

Mr. CONTE. Where are your five dental research institutes and centers located? How are you disseminating your research findings to the profession?

Dr. KRESHOVER. The five currently supported dental research institutes (centers) are at the Universities of Alabama, Michigan, North Carolina, Pennsylvania, and Washington. As I indicated in my opening statement, Mr. Conte, a major role is being played today by the Institutes in generating a broad collaboration among scientists from a wide number of institutions and science disciplines; as well as in disseminating, through various communications media, the nature of progress of their researches.

BUDGET

Mr. CONTE. You are requesting a net change of about $6 million less than last year. Will you be able to properly carry out your functions at this level of funding? What could you do if you were kept at last year's level?

Dr. KRESHOVER. No, sir, we would have to negotiate type 5 grants and contracts. Direct operations would have to be reduced. Also, career award commitments could not be funded. If maintained at the fiscal year 1975 level, we would, of course, be able to support type 5 commitments and award approximately 51 competing grants.

COST-BENEFIT PROGRAMS

Mr. CONTE. In your justification, one of the objectives for 1976 is the analysis of new control measures in the context of costs, benefits, and acceptance. Would you elaborate?

Dr. KRESHOVER. Quite obviously, sir, caries prevention methods must not only be effective, but also must be feasible of application or delivery. This being the case, we have to undertake careful study and collection of data on community acceptance, economics, and personnel requirements of public health caries prevention programs. As I am sure is recognized by this subcommittee, the collection of such data is expensive and requires extensive use of consultants outside of the usual biomedical research community.

UNFUNDED GRANTS

Mr. CONTE. How many approved but unfunded research grants will you have this year? How many more grants could you fund at the 1976 level of appropriations?

Dr. KRESHOVER. At the present time, Mr. Conte, we have estimated that we will have 84 unfunded research grants in the aggregate amount of $3,991,000. In addition, I believe that no more than 51 new grants, shown in our budget justification, would be funded since additional funds would be required to support type 5 commitments.

Mr. CONTE. Thank you, Mr. Chairman.

Mr. FLOOD. Thank you, Dr. Kreshover.

Dr. KRESHOVER. Thank you, Mr. Chairman.

JUSTIFICATION OF THE BUDGET ESTIMATES

Appropriation Estimate

NATIONAL INSTITUTE OF DENTAL RESEARCH

For expenses not otherwise provided for to carry out title IV, parts C and I of the Public Health Service Act, [$49,864,000.] $43,536,000.

For the National Institute of Dental Research for the period July 1, 1976, through September 30, 1976, $7,924,000.

Amounts Available for Obligation 1/

	1975 Estimate	1976 Estimate
Appropriation	$49,864,000	$43,536,000
Comparative transfer to:		
"Office of the Director, NIH" (Transfer of the Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	-9,000	---
"Research Resources" (Transfer of support for Rhesus Monkey supply program)	-22,000	---
Total, obligations	49,833,000	43,536,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1974 - $6,000; 1975 - $6,000.

Summary of Changes

1975 Estimated obligations	$49,833,000
1976 Estimated obligations	43,536,000
Net change	-6,297,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Extra day of pay in 1976.		--		+$26,000
2. Within grade increases...		--		+85,000
3. Other (increase in BEC, FTS, Postage, Health Benefits, and FICA).....		--		+15,000
4. Annualization of 1975 pay increase.....		--		+142,000
Subtotal.....		--		+268,000
B. Program:				
1. Research grants:				
a. Noncompeting continuations.....		$9,205,000		+8,701,000
b. Competing.....		--		+2,659,000
c. Special.....		800,000		+7,000
2. Continuation costs from Multi-year funding in previous years:				
a. Regular Research grants.....		--		+1,747,000
b. Training grants.....		--		+505,000
c. Contracts.....		--		+320,000
3. Fellowships.....		2,900,000		+333,000
Subtotal.....		--		+14,272,000
Total, increases....		--		+14,540,000
Decreases:				
A. Built-in:				
1. Payment to the NIH Management fund.....		--		-160,000
Subtotal.....		--		-160,000
B. Program:				
1. Research grants:				
a. Noncompeting completed, converted, or terminated.....		9,205,000		-9,643,000
b. Competing.....		8,701,000		-8,701,000
c. Special.....		800,000		-110,000
2. Fellowships.....		2,900,000		-33,000
3. Training.....		2,869,000		-1,077,000
4. Contracts.....		4,171,000		-566,000
5. Caries.....	34	1,406,000	--	-227,000
6. Intramural Laboratory and clinical research...	169	8,372,000	-4	-120,000
7. Research management and program services....	69	3,217,000	--	-200,000
Subtotal.....	--	--	-4	-20,677,000
Total, decreases.....	--	--	-4	-20,837,000
Total, net change.....	--	--	-4	-6,297,000

Explanation of Changes

Increases:

A. Built-in: These increases will provide: 1. $26,000 for one extra day of pay in 1976, $18,000 for Intramural Laboratory and Clinical Research, $6,000 for Research Management and Program Services, and $2,000 for Caries Direct Operations; 2. $85,000 for within grade pay increases, $55,000 for Intramural Laboratory and Clinical Research, $20,000 for Research Management and Program Services, and $10,000 for Caries Direct Operations; 3. Other increases of $15,000 — $1,000 for Bureau of Employee Compensation, $3,000 for increased costs of FTS, $3,000 for increased costs of postage, $4,000 for annualization of Health Benefits and $3,000 for increased costs of FICA in Intramural Laboratory and Clinical Research and $1,000 for annualization of Health Benefits in Research Management and Program Services; 4. $142,000 for annualization of 1975 pay increases, $102,000 in Intramural Laboratory and Clinical Research, $26,000 in Research Management and Program Services, and $14,000 in Caries Direct Operations.

B. Program:

1. Research Grants:
   a. The increase of $8,701,000 in noncompeting research grants represents noncompeting requirements resulting from grants awarded in 1975.
   b. The amount of $2,659,000 represents new awards, and competing continuations from previous years.
   c. The increase of $7,000 represents an increase in funding of the Scientific Evaluation Grant.
2. Multi-year funds:
   a. The increase of $1,747,000 in regular research grants represents continuation costs resulting from multi-year funding in 1974.
   b. The increase of $505,000 in training grants represents continuation costs resulting from multi-year funding in 1974.
   c. The increase of $320,000 in research and development contracts represents continuation costs resulting from multi-year funding in 1974.
3. Fellowships: Increase in fellowships represents stipend of $333,000 for the Fellowship program.

Decreases:

A. Built-in: The decrease of $160,000 represents a decrease to the NIH Management fund for centrally furnished services.

B. Program:

1. Research Grants:
   a. The decrease of $9,643,000 for noncompeting research grants represents grants that are being converted to competing status and commitments that will not be funded in 1976.
   b. The decrease of $8,701,000 represents the completion or conversion of competing grants to a noncompeting status in 1976.
   c. The decrease of $110,000 in special grants represents commitments that will not be funded in 1976.
2. Fellowships: The decrease of $33,000 reflects reduced funding requirements for "old" fellowship program.
3. Training: The decrease of $1,077,000 relates to the phase-out of the "old" training program.
4. Contracts: The decrease of $566,000 reflects a reduction in continuing requirements and commitments that will not be funded in 1976.
5. Caries: The reduction of $227,000 represents a decrease in operating costs in 1976.
6. Intramural Laboratory and Clinical Research: The reduction of $120,000 represents a decrease in operating costs for 1976.
7. Research Management and Program Services: The reduction of $200,000 represents a decrease in operating costs in 1976.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
137	Caries	34	$10,535,000	34	$8,140,000	---	-$2,395,000
139	Periodontal and Soft Tissue Diseases		9,081,000		7,060,000		-2,021,000
141	Restorative Materials		2,329,000		2,245,000		-84,000
143	Craniofacial Anomalies		7,499,000		6,098,000		-1,401,000
145	Pain Control and Behavioral Studies		1,600,000		1,500,000		-100,000
147	Dental Research Institutes		7,200,000		7,200,000		---
149	Intramural Laboratory and Clinical Research	169	8,372,000	165	8,212,000	-4	-160,000
152	Research Management and Program Services	69	3,217,000	69	3,081,000	---	-136,000
	Total obligations	272	49,833,000	268	43,536,000	-4	-6,297,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	272	268	-4
Full-time equivalent of all other positions	41	41	---
Average number of all employees	316	312	-4
Personnel compensation:			
Permanent positions	$5,457,000	$5,655,000	+$198,000
Positions other than permanent	566,000	585,000	+19,000
Other personnel compensation	47,000	48,000	+1,000
Total personnel compensation	6,070,000	6,228,000	+218,000
Personnel benefits	893,000	938,000	+45,000
Travel and transportation of persons	258,000	226,000	-32,000
Transportation of things	55,000	30,000	-25,000
Rent, communications & utilities	265,000	196,000	-69,000
Printing and reproduction	75,000	67,000	-8,000
Other services:			
Project contracts	4,821,000	4,575,000	-246,000
NIH management fund	2,589,000	2,429,000	-160,000
Other	1,122,000	986,000	-136,000
Supplies and materials	988,000	878,000	-110,000
Equipment	681,000	522,000	-159,000
Grants, subsidies & contributions	32,017,000	26,405,000	-5,612,000
Deduct quarters and subsistence charges	-3,000	-4,000	-1,000
Total obligations by object	49,833,000	43,536,000	-6,297,000

Significant Items in House and Senate
Appropriation Committee Report

Item	Action Taken or to be Taken
1975 Senate Report	
1. The Committee notes that prospects of an 80 percent reduction in caries offered by techniques under present study is encouraging, but once again stresses the need for the NIDR to utilize and disseminate vital information relating to caries.	1. The NIDR continues to sponsor the the publication of "Advances In Caries Research." The Institute has also developed a state-of-the-art film on the prospects of a caries vaccine, which has been shown at the annual meeting of the American Dental Association and which is now available for free loan to dental schools and dental societies. Planned demonstration projects on preventive procedures will provide further opportunities to disseminate information to the public.
2. In the area of malformations, important data has come from studies of experimental surgical procedures and wound healing. These now provide a basis for the development of treatment techniques leading to better control of bone growth in the rehabilitation of victims of congenital oral-facial anomalies and the Committee recommends that new initiatives be conducted in this area with a portion of increased funds provided by the Congress.	2. The craniofacial anomalies research supported by the Institute during the year focused on improving treatment and understanding basic disease mechanisms as an approach toward the eventual prevention of developmental aberrations in man. Recently reported studies of wound healing after surgical intervention indicate that simulated palatal surgery on young animals drastically reduces skeletal growth on the operated side as compared to the unoperated side. Through studies of this type, it may be possible for surgeons to avoid undesirable side effects.

Authorizing Legislation

Legislation	1976 Authorization	1976 Appropriation Requested
Public Health Service Act		
Section 301—Research and Investigation, in general	Indefinite	$38,039,000 2/
Title IV, Part C--National Institute of Dental Research	Indefinite	
Title IV, Part I--National Research Service Award Act	1/	5,497,000 2/

1/ Authorization expires June 30, 1975, extension legislation is proposed.

2/ Funding estimate only.

National Institute of Dental Research

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$21,275,000	$21,275,000	$22,593,000	$22,692,000
1967	23,752,000	27,198,000	27,198,000	27,198,000
1968	28,982,000	28,982,000	30,744,000	28,978,000
1969	29,189,000	28,328,000	29,191,000	28,758,000
1970	28,064,000	28,064,000	30,654,000	29,658,831
1971	33,575,000	34,054,000	35,054,000	34,198,000
1972	37,890,000	40,757,000	43,757,000	42,317,000
1973	39,280,000	45,805,000	52,814,000	45,805,000 1/
1974	38,417,000	44,096,000	46,965,000	43,924,000 2/
1975	43,928,000	44,357,000 3/	50,969,000	49,833,000
1976	43,536,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

National Institute of Dental Research

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$22,177,000	$22,177,000	$23,677,000	$23,677,000
1967	24,884,000	28,308,000	28,308,000	28,308,000
1968	30,307,000	30,307,000	32,307,000	30,307,000
1969	30,414,000	29,553,000	30,414,000	29,983,500
1970	29,289,000	29,289,000	32,000,000	30,808,800
1971	34,563,000	35,257,000	36,257,000	35,440,000
1972	38,829,000	41,828,000	44,948,000	43,388,000
1973	44,415,000	46,991,000	54,000,000	46,991,000 1/
1974	38,452,000	44,131,000	47,000,000	43,959,000 2/
1975	43,959,000	44,388,000 3/	51,000,000	49,864,000
1976	43,536,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

Justification

National Institute of Dental Research

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	272	$6,963,000	268	$7,226,000	-4	+$263,000
Other expenses	---	42,870,000	---	36,310,000	---	-6,560,000
Total	272	49,833,000	268	43,536,000	-4	-6,297,000

General Statement

As the chief sponsor of dental research and related training in the United States, the Institute encompasses a broad field of activities and studies, ranging from causes of dental and other oral diseases to the development and application of more effective therapeutic and preventive measures.

Because of their complexity, oral problems must be attacked through a comprehensive program of laboratory, clinical, field, and epidemiological studies in such varied areas as developmental biology, genetics, microbiology, virology, materials science, pharmacology, and physiology. In fact, today over 30 scientific disciplines are contributing to an ever-growing base of information on which NIDR is building improved means to treat and prevent oral disease.

Prevention is of crucial importance in dentistry because, unlike medicine's brilliant successes with cures, oral health problems are largely irreversible. The major programs of NIDR are concerned with dental caries (tooth decay); periodontal (gum) disease; problems of growth and development, especially cleft lip and palate and malocclusion; and a variety of oral lesions affecting the tongue, cheeks, and lips. Other areas of emphasis are the development of improved restorative materials, including successful tooth transplants and implants, and pain control.

Dental Research Institutes/Centers were designed as experimental mechanisms to focus the appropriate resources of the parent universities upon the problems of oral health in ideal research and training environments. It was intended that these carefully structured and nurtured Institutes/Centers be attractive to investigators and students from disciplines not generally associated with dental research, thus providing the broad expertise essential to the solution of fundamental problems of dental diseases. NIDR annually awards a special research grant to each of five universities to support five Institutes/Centers.

In 1971, additional funds were authorized to develop the National Caries Program. The NCP, NIDR's most highly developed targeted program, is designed to develop techniques that can eliminate dental caries and be successfully introduced into public health practices. The general NCP strategy is to develop agents that inactivate the microbial process of caries, that increase the resistance of the tooth to caries, or that decrease the potential of the diet to support caries. As a fourth element, the strategy includes the development of information on public health acceptance of new agents and programs. The long-range objective is an evolving armamentarium of control measures that will optimally fit the different needs of children and other population groups.

Periodontal (gum) disease ranks as a major oral health problem. Actually, it is a group of diseases, rather than a single entity. The usual onset, which may occur as early as childhood or adolescence, is known as gingivitis, or inflamed gums. With good oral hygiene, most of the early cases can be reversed. As the disease progresses, however, reversal is less likely. If the disease is allowed to progress unchecked, it results in destruction of the bone supporting the teeth, with the eventual loss of the teeth.

Treatment of periodontal disease is time consuming, costly, and frequently unsuccessful. It remains essentially unavailable to the majority of the population because of its high cost and because of the shortage of periodontists. Thus, to eliminate the harmful effects of this disease and thereby improve the quality of life, it is necessary to develop preventive measures easy enough for everyone to employ.

In February, NIDR began a formal evaluation of its periodontal disease research activity, including both extramural and intramural endeavors. Inas- much as this is the first comprehensive evaluation of an NIDR research program, it will be approached with sufficient flexibility of design to possibly serve as a reasonable model for evaluation of other program areas, and thereby allow for comparative judgements.

The control of herpes simplex virus infections and other oral ulcerative diseases is an important research target. NIDR believes that better diagnosis, control, and prevention of herpes simplex virus infections can be realized within a forseeable period through more intensified research. Recent significant advances in viral immunology may well provide new approaches to the treatment of herpes simplex virus infection and may offer clues for the development of an effective vaccine.

The goals of the craniofacial anomalies research program are to support research and research training to gain knowledge related to the etiology, pathology, prevention, and treatment of craniofacial malformations. This includes such congenital deformities as cleft lip/palate and other syndromes, acquired malformations from surgery or accidents, and malocclusion. The concept of centers for the study of craniofacial anomalies will be under exploration. Through centers, it may be possible to achieve a cohesive effort in investigations of all congenital craniofacial anomalies.

The allocation of resources among the categorical programs utilizing research grants, contracts, training and fellowships as instruments or support, is based on a myriad of factors including program needs; scientific merit; program relevance; and most promising areas in terms of research progress and accomplishments. Advice is provided by the Institute's senior management group and external advisors outstanding in their fields of science. State-of-the-art studies and periodic studies-in-depth of each categorical program with formal presentations by the program chief to the Director also provide vital input. All of these elements are weighed against the Institute's goals and mission before the Director makes the final decisions on allocation of resources.

DHEW - National Institutes of Health

CROSSWALK - 1975 Column of 1976 President's Budget

INSTITUTE: National Institute of Dental Research
(In Thousands)

Program	Research Grants: Regular Program Noncompeting	Research Grants: Regular Program Competing	Research Grants: Specials Multi-disciplinary Centers	Research Grants: Other	Training Programs: Grants	Training Programs: Fellowships	Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
1. Caries.....	2,504	2,760		197	291	464		2,913	1,406	10,535
2. Periodontal and Soft Tissue Diseases....	3,055	3,176		290	877	967		716		9,081
3. Restorative Materials.....	744	355		87	476	100		567		2,329
4. Craniofacial Anomalies.....	2,739	2,002	342	180	805	1,031		400		7,499
5. Pain Control and Behavioral Studies.	163	408		46	420	338		225		1,600
6. Dental Research Institutes.....			7,200							7,200
7. Intramural Laboratory and Clinical Res...							8,372			8,372
8. Research Management and Program Srv....									3,217	3,217
Total obligations.....	9,205	8,701	7,542	800	2,869	2,900	8,372	4,821	4,623	49,833

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN OF 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute of Dental Research

(In Thousands)

Program	Research Grants: Regular Program Non-competing	Research Grants: Regular Program Competing	Research Grants: Specials Multi-disciplinary Centers	Research Grants: Other	Training Programs: Grants	Training Programs: Fellowships	Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
1. Caries	2,711	660		182	94	513		2,717	1,263	8,140
2. Periodontal and Soft Tissue Diseases	3,593	846		246	654	1,055		666		7,060
3. Restorative Materials	757	269		87	469	96		567		2,245
4. Craniofacial Anomalies	2,750	725	342	136	593	1,152		400		6,098
5. Pain Control and Behavioral Studies.	199	159		46	487	384		225		1,500
6. Dental Research Institutes			7,200							7,200
7. Intramural Laboratory and Clinical Res							8,212			8,212
8. Research Management and Program Srv									3,081	3,081
Total obligations	10,010	2,659	7,542	697	2,297	3,200	8,212	4,575	4,344	43,536

NATIONAL INSTITUTE OF DENTAL RESEARCH
MECHANISM TABLE
(In thousands)

	FY 75		FY 76	
	No.	Amount	No.	Amount
GRANTS				
Research Grants:				
Non-competing	160	$9,205	168	$10,010
Competing	57	3,700	23	1,259
New	99	4,601	28	1,000
Supplemental	(12)	400	(12)	400
Subtotal	316	17,906	219	12,669
Special:				
Specialized research centers	1	342	1	342
Dental Research Institutes	5	7,200	5	7,200
Research Career Program	33	752	28	642
Scientific Evaluation	1	48	1	55
Subtotal	40	8,342	35	8,239
Fellowships:				
Non-competing	66	1,803	91	3,200
Competing	0	0	0	0
New	27	1,097	0	0
Supplemental	0	0	0	0
Subtotal	93	2,900	91	3,200
Training:				
Non-competing	48	2,869	34	2,297
Competing	0	0	0	0
New	0	0	0	0
Supplemental	0	0	0	0
Subtotal	48	2,869	34	2,297
DIRECT OPERATIONS:				
Intramural Labs and Clinic	--	8,372	--	8,212
Collaborative Research and Support	--	1,406	--	1,263
Research and Development Contracts	--	4,821	--	4,575
Research Management and Program Services	--	3,217	--	3,081
Subtotal	--	17,816	--	17,131
Total	--	49,833	--	43,536

Caries

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	34	$969,000	34	$995,000	---	+$26,000
Other expenses		9,566,000		7,145,000		-2,421,000
Total	34	10,535,000	34	8,140,000		-2,395,000
Budget Mechanism:						
Research Grants						
Regular						
Noncompeting		$2,504,000		$2,711,000		+$207,000
Competing		2,760,000		660,000		-2,100,000
Special		197,000		182,000		-15,000
Training Programs						
Training Grants		291,000		94,000		-197,000
Fellowships		464,000		513,000		+49,000
Research and Development						
Contracts		2,913,000		2,717,000		-196,000
Other		1,406,000		1,263,000		-143,000
Total		10,535,000		8,140,000		-2,395,000

Objectives, 1976:

In 1971, additional funds were authorized to develop the National Caries Program, a highly coordinated effort seeking to develop techniques that can eliminate dental caries and be successfully introduced into public health practice.

The general NCP strategy is to develop agents that inactivate the microbial process of caries, that increase the resistance of the tooth to caries, or that decrease the potential of the diet to support caries. As a fourth element, the strategy includes the development of information on public health acceptance of new agents and programs. The long-range objective is an evolving armamentarium of control measures that will optimally fit the different needs of children and other population groups.

The most promising approaches to caries control appear to be antiplaque agents released slowly in the mouth, polymer sealants for the deep pits and fissures of the posterior teeth, new techniques to obtain fluorapatite formation deep within the tooth and, as a more long-range prospect, vaccination. These are the dominant areas of expansion in NCP plans for FY 1976. Increasing emphasis will be given to analysis of new control measures in the context of costs, benefits and acceptance.

Accomplishments 1975:

Dental caries is a localized, progressive destruction of the teeth initiated by acid demineralization of the outer tooth enamel. It results from a complex interaction among three factors: bacterial agents, dietary environment and tooth susceptibility. The general operating plan of the National Caries Program embraces four major objectives or strategies.

I. To inhibit the microbial process. The unique characteristics of cariogenic bacteria that enable them to adhere to the surface of teeth and to form tooth destroying acids are major targets of program-supported research. Immunization and antimetabolites are two approaches being developed to block formation of bacterial adhesives; enzyme mixtures are being evaluated to reduce bacterial plaque on teeth; and bacteriostatic agents are being screened for public health use in controlling plaque bacteria and thereby reducing acid formation. About one-half of total Program support is in these areas.

In FY 1975, there was expansion of research with rats and monkeys to determine the feasibility of a caries vaccine, pre-clinical screening and short- term clinical trials of promising anti-plaque agents, and research concerned with the difficult problem of preventing decay of the roots of teeth when gums recede in older individuals. In addition, new research was supported to explore methods for improved delivery of agents to the surface of the tooth and for slow continuous release of anticaries agents in the mouth.

II. To increase the resistance of the tooth. The caries process involves destruction of tooth mineral by bacterial-generated acids. The rate at which dissolution takes place depends, in a complex fashion, on the mineral composition and microscopic structure of the tooth surface and on the microbial plaque. Extensive efforts are underway to establish techniques for introducing fluoride and other elements into the smooth surface areas of teeth to seal microscopic pores and develop mineral phases that resist acid destruction. Also, several trials to evaluate, under field conditions, the effectiveness of polymer films for sealing the pit and fissure areas of posterior teeth are now nearing completion.

In FY 1975 the Program supported research to produce detailed information on the physiochemical events in caries and on the mechanisms of fluoride anticaries effects. It is expanding its support of research to develop polymer films which adhere more tightly and can be applied more easily to the tooth surface compared to currently available films.

III. To decrease the cariogenic potential of the diet. Caries control through decreased consumption of sucrose is made difficult because of public predilection for sweet foods, patterns of snack food consumption and food processing with sucrose-type sugar. Recently concluded animal trials strongly suggest that on a long-term basis the substitution of other sugars for sucrose will not significantly lower the cariogenicity of the diet. Current research seeks alternative noncariogenic sweetners. Also, research on early caries detection has been expanded.

IV. To develop methods to improve delivery and acceptance of caries prevention techniques. If dental caries as a national health problem is to be successfully resolved through use of techniques developed by the Program, a crucial factor will be acceptance and utilization by the public. Many factors will affect utilization, such as perceived health state and benefits, costs to individuals and communities, and attractiveness of use. Thus, to enable prediction of the cost and effectiveness of alternative routes to caries control and to insure success in having new agents widely accepted, the Program currently is supporting three large studies with school children in which data on costs, benefits and effectiveness of counseling programs is being examined.

New research was begun to determine why some children are much more concerned about personal oral health than others. Research on health communication and motivation and on techniques for predicting costs and benefits of new programs was also expanded.

Periodontal and Soft Tissue Diseases

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Other expenses.....		$9,081,000		$7,060,000		-$2,021,000
Budget Mechanism:						
Research Grants						
Regular						
Noncompeting.....		$3,055,000		$3,593,000		+$538,000
Competing.....		3,176,000		846,000		-2,330,000
Special.....		290,000		246,000		-44,000
Training Programs						
Training Grants.....		877,000		654,000		-223,000
Fellowships.....		967,000		1,055,000		+88,000
Research and Development						
Contracts.....		716,000		666,000		-50,000
Total.....		9,081,000		7,060,000		-2,021,000

Objectives, 1976:

The ultimate mission of the Periodontal and Soft Tissue Diseases Program is to develop new knowledge which may ultimately lead to the prevention and eradication of these diseases.

Continued emphasis will be placed on defining the numerous steps in the periodontal disease process itself, as well as other soft tissue lesions, in order to develop more rational means for their prevention and control. Ongoing and new studies will attempt to develop both fundamental and practical knowledge on all of the biological events involved in these disease processes, from the earliest attachment of bacteria to the tooth or gums to the ensuing immune inflammatory responses associated with tissue destruction. Because adherence of bacteria to teeth or to soft tissue is important in initiating infection, special emphasis will be given to this area. In view of the recent isolation of new organisms highly suspected of being periodontal pathogens, studies will be done to characterize these organisms and relate them to disease. Meanwhile, efforts to clarify the role of immune mechanisms in periodontal and soft tissue diseases will continue, as well as specific studies on the biochemistry of periodontal connective tissue components. Research to identify and test various chemotherapeutic agents for efficacy in preventing plaque or inhibiting bone destruction will also be sustained.

Increased programming efforts will also be made to stimulate research dealing with aphthous ulcers, herpes virus infections, and oral cancer. In particular, research will focus on developing better diagnostic methods and suitable therapy for herpes simplex virus infections. The ultimate objective is to develop a vaccine for prevention. In order to develop a more cohesive program on the problems of oral cancer continuing effort will be made to coordinate NIDR activities with those of the regional cancer centers and other programs of the National Cancer Institute.

Accomplishments, 1975:

Periodontal Disease

To achieve an understanding of the disease processes in periodontal disorders, research has concentrated on pathogenesis, host response and the mechanisms of

tissue destruction. Significant attention has also been devoted to etiologic factors, mainly in the area of microbiology and dental plaque formation.

Since the dentobacterial plaque is thought to initiate the chain of events leading to inflammation and bone destruction, etiologic studies have emphasized its role in disease. In the last few years, efforts to identify pathogenic bacteria have become systematic and comprehensive. It is now becoming clear that different forms of periodontal disease may be caused by different bacteria. In studies this past year, scientists discovered a new group of oral organisms which appear to be the primary cause of an extremely severe form of periodontal disease in which the bone supporting the teeth is rapidly destroyed. Related studies showed that these organisms would cause the same type of rapid alveolar bone destruction when germ-free rats are infected with them. Significant new progress has also been made in identifying biological mechanisms of alveolar bone resorption in the human host, and in testing chemical substances to inhibit the resorption. In addition, new information has shown that the net loss of connective tissues observed in periodontal disease is probably the result of depressed formation as well as enhanced degradation of tissue. Emerging evidence indicates that the inflammatory process offers mechanisms which bring about both of these effects. Efforts to develop suitable animal models for periodontal disease studies have been encouraging. Although research efforts dealing with the prevention and treatment of periodontal disease have been at a low level in the past, studies of the etiology and pathogenesis of the disease have yielded sufficient new data upon which to base increased future efforts directed specifically toward developing improved preventive or therapeutic measures.

Oral Cancer

Studies of the various mechanisms involved in the spread of cancer throughout the body are being examined in experimental animal systems with special emphasis on the regulatory role of the hosts' immune systems. A related study involving oral tumors in dogs confirmed previous reports that the early immune response to neoplasia tends to stimulate rather than to inhibit tumor growth. Efforts to increase research activity in oral cancer have resulted encouraginly in a number of new grant applications. It is hoped that these recently received proposals will set the stage for much needed expansion in the oral cancer programs of the NIDR and the NCI.

Oral Soft Tissue Diseases

The control of herpes simplex virus infections and other oral ulcerative diseases is an important research target. NIDR believes that better diagnosis, control, and prevention of herpes simplex virus infections can be realized within a forseeable period through more intensified research. Recent significant advances in viral immunology may well provide new approaches to the treatment of herpes simplex virus infection and may offer clues for the development of an effective vaccine. During the past year studies of human subjects susceptible to herpes infection showed that herpes simplex virus causes a depression in the cellular immune defense mechanism of the body. In an attempt to discover an effective vaccine against herpes simplex virus, a group of investigators are analyzing and purifying antigens produced during active infections with this virus. It is believed that increased research with modern sophisticated methods may reveal the causes of other common painful oral ulcerative diseases, such as recurrent aphthous ulcers. With this knowledge, additional research can be initiated to develop the means to control these diseases. Related new studies in the area of oral host/parasite interactions demonstrate that salivary glycoproteins can prevent the adherence of specific bacteria to the oral mucous lining.

Restorative Materials

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Other expenses.....		$2,329,000		$2,245,000		-$84,000
Budget Mechanism:						
Research Grants						
Regular						
Noncompeting.....		$744,000		$757,000		+$13,000
Competing.....		355,000		269,000		-86,000
Special.....		87,000		87,000		---
Training Programs						
Training Grants.....		476,000		469,000		-7,000
Fellowships.....		100,000		96,000		-4,000
Research and Development						
Contracts.....		567,000		567,000		---
Total.....		2,329,000		2,245,000		-84,000

Objectives, 1976:

Since the highly specialized tissues of the mouth cannot replace themselves when they are lost, treating the effects of dental disease is still largely based upon the effective use of available materials. Therefore, the principal objectives of the Restorative Materials Program are to provide better dental care by fostering the development of improved materials and methods to replace lost tissues and to restore normal form and function.

Efforts will be continued to improve amalgams, composite resins, and other filling and adhesive materials. Special emphasis is being given to research on artificial dental implants and projects to develop better maxillofacial prostheses. Through contract mechanisms the research and development of implants is being approached more systematically. In one contract the influence of tooth design on implant acceptability is being studied in animals. In this study the effects of tooth shape, as well as the effects of grooves, slots, and porosity, are being evaluated. In two other studies, the influence of the chemical composition of the tooth implant is being assayed. Artificial teeth made of ceramic, metal, and plastic are being tested under these contracts.

Accomplishments, 1975:

The Restorative Materials Program supports research in five broad categories: restorative materials for repairing the damage from dental diseases; plastic adhesive sealants for protecting the surfaces of teeth against decay and for sealing the margins of fillings; maxillofacial prostheses for replacing defective tissue resulting from birth defects, accidents, or surgery; artificial tooth implants to provide either serviceable replacements for missing teeth, or posts to anchor bridges or complete dentures in place; and development of devices, equipment, and standards for materials testing.

The study of marine animal adhesives has been completed with the partial analysis and preliminary characterization of the proteinaceous cement secretions of barnacles and mussels. Since tests of retention indicate that synthetic products

currently available are as good as these marine materials, only limited studies on marine animal adhesives will be continued. In the meantime, promising synthetic elastomeric liners for cavity preparations are being evaluated in dogs and monkeys, utilizing composite and amalgam restorations.

During the past year new contracts have been let to fill voids in grant-supported research on implants and maxillofacial prostheses. Studies on implants are attempting to determine the relative importance of the materials, as well as the importance of root designs in the acceptance of the implants. In the projects on maxillofacial prostheses, contractors will develop and test materials specifically for use as artificial skin in humans.

Nine studies of endosseous tooth implants are being currently funded. Experimental implants of several designs fabricated from different materials are being tested in baboons, dogs and swine. The designs range from solid blades to porous tooth root replicas, and the materials include polymethyl methacrylate, calcium aluminate, vitreous carbon, "bio-glass" and titanium. Illustrative of progress from earlier initiated research, specimens of sintered titanium wire in the shape of cylinders have remained firm for up to 24 months after implantation in the mouths of baboons. In another study it was shown that porous metal composite implants made of titanium-aluminum-vanadium in a cylindrical form were successfully retained in the mandibles of swine.

Work conducted under an interagency agreement has shown progress in standardizing a laboratory procedure for measuring the potential functional wear of restorative materials. This work is significant because it may enable scientists to accurately determine the wear characteristics of new materials without having to resort to long term, expensive clinical testing.

Craniofacial Anomalies

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Other expenses.....		$7,499,000		$6,098,000		-$1,401,000
Budget Mechanism:						
Research Grants						
Regular						
Noncompeting.....		$2,739,000		$2,750,000		+$11,000
Competing.....		2,002,000		725,000		-1,277,000
Special.....		522,000		478,000		-44,000
Training Programs						
Training Grants.....		805,000		593,000		-212,000
Fellowships.....		1,031,000		1,152,000		+121,000
Research and Development						
Contracts.....		400,000		400,000		---
Total.....		7,499,000		6,098,000		-1,401,000

Objectives, 1976:

The goals of the Craniofacial Anomalies Program are to gain knowledge related to the cause, pathology, prevention, and treatment of craniofacial malformations. This includes such congenital deformities as cleft lip/palate and other syndromes, acquired defects from surgery or accidents, and malocclusion of teeth and jaws.

The concept of Centers for studying in a coordinated way all types of craniofacial anomalies will be explored. This is timely because of the recent breakthrough in surgical treatment of severe craniofacial deformities and the achievements of interdisciplinary research within the cleft palate centers. In addition, studies of wound healing after experimental corrective jaw surgery in animal model systems will establish measurements of nerve and blood vessel renewal and growth patterns of healing tissues. The mechanisms by which growth in the face and head region is altered by orthopedic measures will be explored in animal research. Although giant steps have been made in embryology, the precise timing of various stages of cellular differentiation and migration has not been determined in human development. Recent advances make it possible to study migration of labeled cells from the neural crest of the embryo into regions which will become the mouth and face. Other studies will focus on drugs, enzyme activities, and environmental factors that may interfere with palatal closure. These experiments will be made with laboratory animals.

During FY 1976, new projects will explore the role of vascularization during craniofacial development, the alteration of epithelial surfaces prior to contact of palatal shelves and subsequent epithelial fusion, and the cell recognition and cell death which normally occur during palatal development. Studies will be initiated to identify the neuro-muscular activity alteration in response to various stimuli which have been shown to produce dento-skeletal alteration and malocclusion. These studies should offer insight into potential mechanisms of malocclusion development.

A workshop on Craniofacial Anomalies Classification and Nomenclature will be conducted to formulate biologically meaningful guidelines to promote uniformity within the field of malformation communication. Workshops will also be conducted on the Psychosocial Aspects of Craniofacial Malformation and on Research on Orthognathic Surgery.

Accomplishments, 1975:

The craniofacial anomalies research supported by the Institute during the year focused on improving treatment and understanding basic disease mechanisms as an approach toward the eventual prevention of developmental aberrations in man.

In basic studies now underway investigators are examining the numerous processes in structural development associated with intercellular interactions, such as cell migration and cell recognition. These interactions are perceived to be related to functions of the outer cell surface and thus are considered fundamental to many developmental problems in craniofacial malformations. Ongoing studies are also unravelling the interactions of the different cells involved in tooth formation.

Advances continue in experimental techniques for studying cleft palate. In one newly devised technique, mouse embryos are exteriorized and immersed in a synthetic fluid while they are still attached to the maternal organism by the umbilical cord. With this technique, it has been possible to directly observe the developing embryo and thus obtain better control of variables of the animal model experiments and improve the study of mechanisms of teratogenesis. One finding obtained with this technique indicated that cortisone produces cleft palate in mice by reducing neuromuscular activity, and thus hindering the normal displacement of the tongue from between the palatal processes. The genetic components in the etiology of human cleft lip and palate were followed in epidemiological studies involving racial groups in Hawaii and in a high risk Haliwa Indian population in North Carolina.

Recently reported studies of wound healing after surgical intervention indicate that simulated palatal surgery on young animals drastically reduces skeletal growth on the operated side as compared to the unoperated side. Through studies of this type, it may be possible for surgeons to avoid undesirable side effects.

Research in the transplantation of viable sutures into areas where sutures are missing (cleft palate) or where sutures have prematurely closed (Apert's Syndrome) represents a very promising potential advancement within the habilitation field. Studies are now involved in the identification of the mechanisms in suture formation.

Research in malocclusion emcompassed both laboratory studies on the basic cellular response to orthodontic treatment and clinical projects on craniofacial growth and oral function. Attempts to define the fundamental stimuli involved in bone formation and resorption have shown that cyclic AMP (adenosine monophosphate) may mediate a signal in mechanically stressed bone. Another project with potential clinical application looked into factors controlling the rate of tooth eruption. By altering the occlusion or by applying physical restraints, the rate of eruption of mouse incisors was accelerated or slowed. Projects concerned with craniofacial growth prediction, biomechanics, and treatment evaluation have improved the diagnosis and treatment of orthodontic problems. One study concluded that a better estimate of a patient's facial growth potential may be determined by examining relatives in the immediate family than by relying on population norms. Another important investigation evaluated orthodontic treatment using the activator appliance. It was found that the activator is most effective in treating malocclusions when used during the transitional dentition.

Pain Control and Behavioral Studies

Authorizing Legislation: Public Health Service Act, Title IV, Parts C and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Other expenses.....		$1,600,000		$1,500,000		-$100,000
Budget Mechanism:						
Research Grants						
Regular						
Noncompeting.....		$163,000		$199,000		+$36,000
Competing.....		408,000		159,000		-249,000
Special.....		46,000		46,000		---
Training Programs						
Training Grants.....		420,000		487,000		+67,000
Fellowships.....		338,000		384,000		+46,000
Research and Development						
Contracts.....		225,000		225,000		---
Total.....		1,600,000		1,500,000		-100,000

Objectives, 1976:

The dual nature of this program, which encompasses pain and behavioral sciences research relevant to dental problems, continues to provide challenge and opportunity. Efforts will continue to increase basic and applied knowledge concerning the etiology, pathophysiology, diagnosis and treatment of the major pain problems of the oral-facial region including the fear and anxiety syndrome generated by the anticipation of pain in dental treatment situations. The behavioral science component of the program deals with efforts to achieve greater understanding and utilization of the many psychosocial factors involved in a wide variety of dental diseases, including their preventive aspects.

High priority will be given to the establishment of multidisciplinary and interdisciplinary oral-facial pain research centers. A joint, cooperative venture with the American Dental Association is being developed to establish discrete anesthesiology and pain control research centers in selected dental schools. The Dental Research Institutes will be utilized as additional resources for pain and behavioral research. Efforts will continue to explore the potential of acupuncture and electrical anesthesia for dental and oral-facial pain control. The pharmacologic aspects of pain control also require further investigation.

In the behavioral sciences area, the problem of more reliable evaluation and more effective handling of dental phobias and associated anxieties will continue to be explored so that better methods for their control and alleviation can be developed. The Pain Control and Behavioral Studies Program will also continue to inventory and coordinate the behavioral content of all NIDR program areas and provide assistance in project development and evaluation. Basic behavioral research projects will be identified to provide information relevant to a variety of dental disease problems.

Accomplishments, 1975:

A. Pain Control - Among the new projects initiated were a major acupuncture study and an oral-facial pain research center.

Significant progress has been reported in understanding the role of psychological and physiological factors in the etiology and treatment of the myofacial pain-dsyfunction (MPD) syndrome. Using computer summation techniques, it was demonstrated unequivocally for the first time that electrical cerebral reactions occurred in response to tooth pulp stimulation. These results promise an improved approach to the study of acute dental pain in man. Studies on the mechanisms of electrical analgesia indicate that this technique may eventually be used to alleviate dental pain. A study on hypnosis in the dental situation has demonstrated that this method can be effective as a dental anesthetic in certain patients. A major cooperative effort with the American Dental Association to foster training and research in pain control in dental schools was successfully initiated and is now in the process of development.

B. Behavioral Studies - With increasing recognition of the importance of the behavioral aspects of many dental problems, efforts continue to utilize the behavioral sciences more effectively in these situations. A comprehensive review is underway of the fear and anxiety syndrome responsible for avoidance of essential dental treatment by millions of individuals. A workshop is planned for the near future to identify new approaches toward a solution of this avoidance phenomenon.

Dental Research Institutes

Authorizing Legislation: Public Health Service Act, Title IV, Part C

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Other expenses.....		$7,200,000		$7,200,000		---
Budget Mechanism:						
Research Grants Special.....		$7,200,000		$7,200,000		---
Total.....		7,200,000		7,200,000		---

Objectives, 1976:

Dental Research Institutes/Centers were designed as experimental mechanisms to focus the appropriate resources of the parent universities upon the problems of oral health in ideal research and training environments. It was intended that these carefully structured and nurtured Institutes/Centers be attractive to investigators and students from disciplines not generally associated with dental research, thus providing the broad expertise essential to the solution of fundamental problems of dental diseases. In accord with these aims, NIDR annually awards a special research grant to each of five universities to support five Institutes/Centers.

This special activity is intended to achieve the most from existing dental research capability and also to develop new manpower resources by challenging scientists from medical, engineering, and graduate schools, as well as other university components. Institutes are expected to build on and extend existing institutional research strengths; provide for participation of multiple disciplines, and facilitate collaboration of a wide range of biological, physical, and social sciences in the study of oral health problems in relation to the program objectives of the NIDR. Interaction with the educational programs of the parent university is encouraged by having an appreciable component of Institute research staff serve as active members of the academic departments representing their fields of competence. Although each Institute requires a permanent staff, participation by other scientists on a temporary or part-time basis is strongly encouraged. Institutes are also encouraged to establish mutually beneficial relationships with other regional resources including educational and research institutions, hospitals, computer facilities, MEDLARS regional centers, and primate centers.

The program will be maintained at the same level in 1976.

Accomplishments, 1975:

In 1975 NIDR will award five research grants, totaling $7,200,000, to five universities for the support of Institutes/Centers. It is not anticipated that there will be major changes of research personnel or research objectives of the Institutes/Centers during the coming year.

The Institute of Dental Research at the University of Alabama has had no major changes in staff or research programs this year. Research emphasis continues to be directed toward periodontal disease and caries with a very strong program in connective tissue research.

The Dental Research Institute at the University of Michigan has undergone a major reorganization under the leadership of its new Director. Its investigators have been grouped into three interdisciplinary teams to tackle three large problem areas of oral health: (1) periodontal disease and caries, (2) viral diseases of the oral cavity, (3) growth and function of the masticatory apparatus.

The Dental Research Center at the University of North Carolina has functioned under the leadership of an Acting Director, while a search committee has continued to seek a new Director. Research at this center has concentrated on growth and development, but a newly developed pain control program has been expanded and strengthened.

The Center for Oral Health Research at the University of Pennsylvania has appointed a new Director. This center has made excellent progress in developing cohesive research units with efforts focused on periodontal diseases and soft tissue studies.

The Center for Research in Oral Biology at the University of Washington has had no significant changes in personnel, and its research continues to be centered on periodontal diseases with related studies of salivary secretions and nutrition.

Intramural Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act, Title IV, Part C

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	169	$4,341,000	165	$4,526,000	-4	+$185,000
Other expenses		4,031,000		3,686,000		-345,000
Total	169	8,372,000	165	8,212,000	-4	-160,000

Objectives, 1976:

The laboratory and clinical research studies of the Institute are concerned with the causes, treatment, control, and prevention of diseases and disorders of the oral cavity and facial region, e.g., dental caries, periodontal disease, oral-facial birth defects, and the investigation of oral-facial pain and appropriate pain control measures to make all necessary dental treatment more acceptable.

In FY 1976, the NIDR plans to expand research efforts in the general area of immunological mechanisms. In the aggregate, these mechanisms determine the susceptibility of the individual to infection and disease. Such "host factors" have now been clearly demonstrated to play specific and essential roles in the etiology and pathogenesis of oral diseases, especially periodontal disease, herpes simplex infections, and aphthous stomatitis. It now appears particularly appropriate to extend and apply our current base of immunological information, heretofore derived primarily from animal experimentation, to the various clinical disease states in man.

The Institute's long standing interest in the nature of dental plaque will receive increased emphasis in programs in microbiology and immunology. The nature of plaque, particularly the complex interaction between the bacteria harbored in plaque, determines its pathogenicity both with respect to dental caries and to periodontal disease. Accordingly, a continuing focus on plaque is essential to understanding both disease states. In conjunction with the National Caries Program applied effort, intramural programs in microbiology will be directed toward resolving the mechanism by which certain bacteria adhere to hard and soft tissues. Microbial enzymes responsible for producing the sticky polysaccharide matrix of plaque are being isolated and used to study the role of local and systemic immunity in the prevention of plaque formation and ultimately may provide an immunotherapeutic approach to the prevention of caries and periodontal diseases.

An increased capacity is planned for dealing with problems of oral and facial pain, i.e., a Neurobiology and Anesthesiology Program has been established to provide much needed basic and clinical research in these areas. The approach to elucidation of problems relating to pain and pain control will continue to be a dual one, i.e., fundamental research in the neurological basis of facial pain, combined with systematic scrutiny of new analgesic and anesthetic agents at the clinical level.

Disordered facial and oral development remains one of the most tragic and difficult problems facing dental research. Laboratory and clinical programs will continue to explore from every point of view the nature of human development both at the cellular and molecular level as well as in experimental animal models and human patients. While primary interest remains that of determining mechanisms responsible for clefting of the lip and/or palate in man (a birth defect occurring in approximately 1 out of 700 live births in the United States), attention must

necessarily also be directed to broader research questions relating to the nature of growth and differentiation, since it is from these inquiries that potential preventive and/or therapeutic techniques may make themselves evident.

A relatively new area of consideration for the Institute involves the systematic analysis of factors influencing the transfer of diagnostic information. This effort is in response to the conspicuous need for better diagnostic methods for early interception of the largely irreversible, insidious pathological processes characteristic of dental diseases. Theoretical assessment of existing diagnostic systems provides a means for better understanding of ultimate limitations of current research efforts while at the same time suggesting alternatives for applying new methodological advances in the management of dental disorders.

Fundamental to the understanding and control of oral disease is the structure of the teeth and the supporting bone and soft tissue. Laboratory programs are increasingly drawing upon basic findings about the nature of the mineral content, the structural proteins, and the carbohydrate constituents of these oral tissues to determine how they are formed, how they function, and how they are affected by disease processes. These studies will provide a rational basis for the treatment of oral disease.

The fever blister or cold sore, caused by herpes simplex virus (HSV), is one of the most common viral infections of man. In addition to oral manifestations, HSV infection of the eye is one of the leading causes of blindness, is the most common non-epidemic cause of viral encephalitis, and can result in death. Another type of HSV is responsible for the second most common venereal disease in the United States and recently has been linked to cancer of the cervix and possibly other tumors, including oral cancer.

The time is ripe to initiate a vigorous program to study this multifaceted disease. First, attempts should be made to determine whether HSV is in fact involved in oral tumors; second, efforts should be made to develop an effective vaccine; and third, clinical trials should be initiated with different chemotherapeutic agents to find more effective ways of treating those patients who are already suffering from this infection.

A second common affliction of the oral cavity is the canker sore or aphthous ulcer. In contrast to the "fever blister," the cause of aphthous ulcers is not known. The disease spans a spectrum from minor to major aphthous, and some scientists believe that Behcet's syndrome with systemic manifestations represents the extreme end of the spectrum. A new program in aphthous ulcers will be initiated to learn about its etiology and pathogenesis. Such an understanding of this disease may very well hold the key to other ulcerative conditions of the skin and gastrointestinal tract (e.g., regional ileitis, ulcerative colitis, etc.).

Accomplishments, 1975:

In Fiscal Year 1975, approximately 114 intramural research projects will be supported at a cost of $8,372,000.

Notable progress has been made in the systematic exploration of host factors in the development of periodontal disease. These immunological mechanisms dictate the host's response to the noxious agent (dental plaque), which is presumed to be responsible for the genesis of periodontal tissue destruction, and so appear to determine the gravity of the disease as well as its course of progression. While it is clear that no periodontal involvement occurs in a mouth free of dental plaque, information regarding the host's reaction to the plaque seems very likely to provide possible routes for preventive measures. Such approaches are essential in combating the disease, since efforts to maintain the mouth in a plaque-free status through conventional educational techniques of oral hygiene appear to be unrealistic.

In another area, laboratory and clinical research into the factors controlling infections by herpes simplex virus have been much expanded. Particularly notable has been the demonstration that the virus is capable of spreading directly from an infected cell to its neighbors without exposing itself to the extracellular environment. This mode of transmission explains in part why the herpes virus is difficult to combat with conventional therapeutic approaches or by the individual's own defense mechanisms, both of which usually depend upon extracellular exposure for their effectiveness.

Clinical research has also continued to be rewarding in the area of salivary gland function, particularly with regard to the utility of minor salivary gland biopsies in diagnosing and assessing therapeutic effectiveness in patients with Sjogren's syndrome.

Research findings concerning the mechanism of synthesis and aggregation of the fibrous protein collagen (the predominant supporting matrix of bones and teeth), which has been the subject of continuing scrutiny at NIDR for a decade, are now being extended to levels of clinical application. A wide variety of genetically determined disease states in man and animals have now been demonstrated to reflect disordered pathways of collagen synthesis or, more frequently, inadequate aggregation of the collagen molecules into functional collagen fibers.

Laboratory studies on the nature and function of the mineral components of oral tissues have resulted in promising advances in two areas. Basic research on the physiochemical interactions between therapeutic agents and tooth mineral has significantly extended understanding of how monofluorophosphate acts as an effective caries preventor. The development and use of quantitiative evaluators of mineral maturity have established correlations between maturational defects in bone and chronic uremia. Similar defects arise upon the administration of massive doses of tetracycline to growing animals.

Finally, basic research on oral-facial mechanisms of pain has led to the development of a model in non-human primates which appears to resemble human behavioral responses to tissue-threatening or tissue-damaging stimuli. Monkeys are trained to escape mildly noxious thermal stimuli applied to their faces in experiments in which they initiate each trial and thus have a measure of control over participation in the experiment. Such research provides a basic framework in which mechanisms of oral-facial pain as well as new behavioral methods of pain control can be studied intensively.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Title IV, Part C

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	69	$1,653,000	69	$1,705,000	--	+$52,000
Other expenses		1,564,000		1,376,000		-188,000
Total	69	3,217,000	69	3,081,000	--	-136,000

Objectives, 1976:

In FY 1976, this activity will continue to provide for the overall administration, direction, and coordination of the Institute's programs.

This activity funds: (1) The Director and his immediate staff concerned with administrative management, scientific and health reporting, financial management, program planning and evaluation, and computer processing services, and (2) the scientific and administrative staff responsible for grant and contract programming, review and administration.

Program direction includes the Institute Director and his immediate staff (executive officer, dental research data officer, program analyst, and equal opportunity specialist and 4 clerical support staff) responsible for the overall management of the Institute's mission. It also includes 12 professional and 19 technical and clerical staff that perform all functions related to financial management, scientific and health reporting, personnel, operations, property management, travel, and all computer processing and analysis activities.

Institute review and approval activities include the Associate Director for Extramural Programs, a Deputy Associate Director, an assistant for special programs, 13 scientific program professionals, and 8 technical and clerical support staff. Personnel of this activity are responsible for the planning and developing of scientific evaluation and fiscal management of the Institute's extramural programs. These responsibilities include development of various mechanisms for support grants in 6 major program areas.

Program area chiefs and their scientist administrators are responsible for all aspects of program planning, administration and individual project and program review which require scientific competency. Technical and clerical staff are required to supplement the efforts of scientific staff in achieving the Institute's goals.

The 1975 workload involved the processing of approximately 449 research grants, special awards, training and fellowship applications totaling in excess of $32 million. The 1976 budget includes 379 awards totaling in excess of $26 million.

Collaborative research includes an Associate Director, a contract specialist, a program management specialist, a staff assistant and 2 clerical support personnel, responsible for development, implementation and evaluation of research and development contracts and agreements. In 1975, 60 contracts and agreements are to be supported for a total amount of $4,821,000. Contracts cover all five activities contained in the budget, i.e., caries, periodontal disease, restorative materials, craniofacial anomalies, and pain control and behavioral studies. The 1976 budget includes 57 research and development contracts costing $4,575,000.

Accomplishments, 1975:

The staff supported by this activity continued to provide administrative management, financial management, program guidance and supportive services to the Institute's staff in the furtherance of the Institute's program to meet its goals.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Caries. (Public Health Service Act, Title IV, Parts C and I)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
34	$10,535,000	Indefinite	34	$8,140,000

Purpose: In 1971, additional funds were authorized to develop the National Caries Program (NCP), a highly organized research and development effort intended to develop methods to eliminate caries as a major health problem.

Explanation: The programs of this activity are carried out by support of research grants, research contracts, graduate training grants, fellowships, research career awards, and direct operations.

Accomplishments in 1975: Dental caries is localized, progressive destruction of the teeth caused by bacteria invading the tooth surface. The disease, causing extensive loss of teeth in school children and young adults, has been reduced in some areas through municipal fluoridation. The National Caries Program is developing techniques to further reduce the incidence of the disease according to four major strategies: (1) combat the microbial agent, (2) increase the resistance of the tooth, (3) modify the diet, and (4) improve the delivery and acceptance of caries preventive techniques. The final stage of research and development for each technique involves several years of field testing and cost-benefit evaluation. A daily mouthrinse with dilute sodium fluoride solution, of particular value for school children exposed to low fluoride drinking water, has satisfactorily passed these tests. The National Caries Program in 1975 launched a nationwide program of projects to demonstrate the technique. The program is being widely publicized. It is expected that many public health officials will visit the demonstration sites and that the observed low cost, simplicity, ease of implementation, and effectiveness of caries prevention achieved by the technique will lead to widespread implementation of similar programs in communities throughout the country.

Approximately 93 research grants, 8 career awards, 13 fellowships, 5 training grants and 37 research and development contracts will be supported in 1975.

Objectives for 1976: Research will continue within the broad framework of the four major program objectives. Some specific objectives for 1976 are: (1) the identification of a safe and effective antiplaque agent, (2) establishment of a valid and reliable primate model for dental caries research, (3) the development of an intra-oral measured release system for the delivery of topical fluoride, and (4) demonstration of the feasibility and effectiveness of school-based caries preventive programs.

Approximately 58 research grants, 7 career awards, 13 fellowships, 1 training grant and 36 research and development contracts will be supported in 1976.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Periodontal and Soft Tissue Diseases. (Public Health Service Title IV, Parts C and I)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$9,081,000	Indefinite	---	$7,060,000

Purpose: The ultimate mission of the Periodontal and Soft Tissue Diseases Program is to develop new knowledge which may lead to the prevention and eradication of these diseases.

Explanation: The programs of this activity are carried out by support of research grants, research contracts, graduate training grants, fellowships, and research career awards.

Accomplishments in 1975: Additional findings supported the contention that different forms of periodontal disease may involve specific bacteria. In a recent study, gram-negative gliding organisms were isolated from patients with a severe form of the disease, and their elimination from diseased human pockets arrested the disease. These organisms produced periodontal bone loss in otherwise germ-free animals. It was also shown that production of a bone resorption factor in cell-mediated immune inflammation requires two types of cells, and that humoral immunity mechanisms in blood can also cause bone to dissolve. Lysosomal enzymes from human leucocytes (white blood cells which defend the body against infection) disrupted the attachment of epithelial cells. Studies of chronic inflammatory disease revealed that sensitized lymphoid cells cause damage to fibroblasts, the cells which produce collagen, and also cause other cells to release collagenase, which breaks down collagen, the chief component of connective tissue and bone. The antimicrobial agent Kanamycin was found to prevent dental plaque and gingivitis in handicapped children for nearly a year.

Studies of oral virus infections showed that the herpes virus reduced the activity of protective leucocytes, a finding which may help to explain the inability of certain individuals to completely rid themselves of the virus.

Approximately 111 research grants, 13 career awards, 34 fellowships, 15 training grants, and 9 research and development contracts will be supported in 1975.

Objectives for 1976: To develop rational means of prevention and control, studies will be made of the biological events involved in the disease processes, from the earliest attachment of microorganisms to the tooth or soft tissue, to the ensuing immune inflammatory responses. New found organisms suspected of being periodontal pathogens will be studied further, as will the role of immune mechanisms and the biochemistry of periodontal tissue components. Expanded research will test the ability of chemotherapeutic agents to prevent plaque or inhibit bone destruction.

Increased efforts will also be made to program research on aphthous ulcers, herpes virus infections, and oral cancer. This research will give special attention to methods of diagnosing and treating herpes infections. Priority will be given to attempts to develop an anti-herpes vaccine.

Approximately 76 research grants, 11 career awards, 33 fellowships, 10 training grants, and 7 research and development contracts will be supported in 1976.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Restorative Materials. (Public Health Service Act, Title IV, Parts C and I)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$2,329,000	Indefinite	---	$2,245,000

Purpose: The objectives of the Restorative Materials Program are to foster the development of new materials and methods for better treatment and prevention of dental and oro-facial disorders and diseases.

Explanation: The programs of this activity are carried out by support of research grants, research contracts, graduate training grants, fellowships, and research career awards.

Accomplishments in 1975: The year was highlighted by successful activity in dental implants. Porous endosseous (bone-penetrating) implants in cylindrical form fabricated of titanium wire have remained firm in baboon jaws for up to 24 months. In another study, cylinders of porous metal composite of titanium, aluminum and vanadium were successfully implanted into the healed tooth sockets of miniature swine. In standardization studies, progress was made in developing procedures to measure wear in restorative materials. Contract research on marine adhesives was terminated after studies had shown little possibility of yielding a superior adhesive useful in dentistry.

Approximately 26 research grants, 2 career awards, 4 fellowships, 8 training grants, and 7 research and development contracts will be supported in 1975.

Objectives for 1976: Efforts will be continued to improve amalgams, composite resins, and other filling and adhesive materials to evaluate different materials and designs for implants, and to develop materials to be used as artificial skin in maxillofacial prostheses.

Approximately 18 research grants, 2 career awards, 4 fellowships, 7 training grants, and 7 research and development contracts will be supported in 1976.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Craniofacial Anomalies (Public Health Service Act Title IV, Parts C and I)

1975			1976	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$7,499,000	Indefinite	---	$6,098,000

Purpose: The objective of this activity is to develop information related to the etiology, pathology, prevention, and treatment of craniofacial malformations.

Explanation: The programs of this activity are carried out by support of research grants, research contracts, graduate training grants, fellowships, and research career awards.

Accomplishments in 1975: Scientists obtained evidence that numerous processes in normal structural development depend upon interactions between cells which may be involved in the development of abnormalities. In a newly devised technique for studying cleft palate, mouse embryos were exteriorized and immersed in a synthetic fluid while they were still attached to the mother by umbilical cord, making it possible to directly observe the embryos. It was found that cortisone causes cleft palate by reducing neuromuscular activity, thus hindering the normal displacement of the tongue from between the palatal processes. Epidemiological studies indicated that a dominant gene may be involved in cases of cleft lip and palate that have a hereditary component. Studies of wound healing showed that palatal surgery reduced skeletal growth on the operated side. Such studies may aid surgeons in avoiding undesirable side effects.

The concept of transplanting viable normal bony sutures into areas where sutures are missing (cleft palate) has now advanced to the point of attempting to make this habilitative procedure a reality.

Approximately 73 research grants, 7 career awards, 34 fellowships, 13 training grants, and 4 research and development contracts will be supported in 1975.

Objectives for 1976: The concept of Craniofacial Anomalies Centers for a comprehensive, cohesive research effort will be explored. Studies of wound healing after experimental corrective jaw surgery in animals will establish measures of the reinnervation, revasularization and growth patterns of healing craniofacial tissues. The mechanisms by which craniofacial growth is altered by orthopedic measures will be explored in animal research on neuro-musculoskeletal interdependence.

Teratogenic studies on cleft lip and palate will continue to focus on the activity of enzymes, drugs and environmental factors involved in palatal closure.

New projects will explore the role of vascularization during craniofacial development, the alteration of epithelial surfaces prior to contact of palatal shelves and subsequent epithelial fusion, and the cell recognition and cell death which normally occur during palatal development. Studies will be initiated to identify the neuro-muscular activity alteration in response to various stimuli which have been shown to produce dento-skeletal alteration and malocclusion. These studies should offer insight into potential mechanisms of malocclusion development.

Approximately 60 research grants, 5 career awards, 33 fellowships, 9 training grants, and 4 research and development contracts will be supported in 1976.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Pain Control and Behavioral Studies. (Public Health Service Act. Title IV, Parts C and I)

1975			1976	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,600,000	Indefinite	---	$1,500,000

Purpose: The objectives of this program are to increase knowledge concerning the nature, etiology, pathophysiology, diagnosis and treatment of oral-facial pain, and to achieve greater utilization of behavioral sciences knowledge in the prevention and treatment of oral-facial diseases and disorders.

Explanation: The programs of this activity are carried out by support of research grants, research contracts, graduate training grants, fellowships, and research career awards.

Accomplishments in 1975: Significant progress was made in the treatment of severe pain in the region of the hinges of the jaw. Analysis of long-term treatment results indicated that conservative, reversible procedures were successful in most patients. Studies on electrical anesthesia and on hypnotic anesthesia showed that these methods could be effective in certain patients under specific conditions.

Approximately 13 research grants, 3 career awards, 8 fellowships, 7 training grants, and 3 research and development contracts will be supported in 1975.

Objectives for 1976: Efforts will be made to identify and involve quality investigators in pain research, and to increase the participation of Dental Research Institutes and Centers in pain and behavioral research. Special meetings will be convened to evaluate the state-of-the-art of pain and behavioral research, and the development of oral-facial pain research centers will be fostered. Studies to explore the potential of acupuncture and electrical anesthesia will continue.

Approximately 7 research grants, 3 career awards, 8 fellowships, 7 training grants, and 3 research and development contracts will be supported in 1976.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Dental Research Institutes. (Public Health Service Act. Title IV, Part C)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$7,200,000	Indefinite	---	$7,200,000

Purpose: The underlying idea of Institutes or Centers is to bring together all of the appropriate resources of the universities and focus these resources upon the problems of oral health in an ideal research and training environment.

Explanation: The programs of this activity are carried out by support of research grants.

Accomplishments in 1975: The strengthening of cohesive, interdisciplinary research teams was emphasized. Within the parent universities 183 collaborative projects were supported, and institute/center scientists participated in 123 collaborative projects with 90 other institutions in the United States and 13 other countries. A total of 493 research papers were published or are in press. Research experience in excellent environments was provided for 94 trainees and 106 research associates.

Objectives for 1976: Multidisciplinary and interdisciplinary collaborative efforts between Institute and Center investigators and scientists from other universities and private institutions in the United States and in foreign countries will continue to be encouraged in the future.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Intramural Laboratory and Clinical Research. (Public Health Service Title IV, Part C)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
169	$8,372,000	Indefinite	165	$8,212,000

Purpose: The laboratory and clinical research studies of the Institute are concerned with the causes, treatment, control, and prevention of diseases and disorders of the oral cavity and facial region, e.g., dental caries, periodontal disease, oral-facial birth defects, and oral soft tissue diseases.

Explanation: Treatment, control, and prevention of oral disorders and diseases are explored through basic and applied research, both in the laboratory and clinical facilities of NIDR.

Accomplishments in 1975: Notable progress has been made in the systematic exploration of host factors in the development of periodontal disease. These immunological mechanisms dictate the host's response to the noxious agent (dental plaque), which appears to be responsible for the genesis of periodontal tissue destruction, and so appears to determine the gravity of the disease as well as its course of progression. It is well established that the typical variety of chronic periodontitis does not occur in a mouth free of dental plaque.

Laboratory and clinical research into the factors controlling infections by herpes simplex virus have been much expanded. Clinical research has also been rewarding in the area of salivary gland function. Basic research findings concerning the mechanism of synthesis and aggregation of the fibrous protein collagen (the predominant supporting matrix of bones and teeth), a subject of continuing scrutiny at NIDR, are now being extended to levels of clinical application.

Objectives for 1976: The NIDR plans to expand research efforts in the general area of immunological mechanisms. These mechanisms determine the susceptibility of the individual to infection and disease. It now appears particularly appropriate to extend and apply our current base of immunological information, heretofore derived primarily from animal experimentation, to the various clinical disease states in man.

The Institute's long-standing interest in the nature of dental plaque will continue to receive emphasis. The nature of plaque, particularly the complex interplay between the microorganisms harbored by plaque, seems to determine its pathogenicity both with respect to dental caries and to periodontal disease. A continuing focus on plaque is essential to better understand both diseases.

A Neurobiology and Anesthesiology Branch, established in 1975, will provide a primary setting for execution of much needed basic and clinical research in oral and facial pain.

Disordered facial and oral development remains one of the most tragic and difficult problems facing dental research. Our primary interest remains that of determining mechanisms responsible for clefting of the lip and/or palate in man since it is from these inquiries that potential preventive and/or therapeutic techniques may make themselves evident.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Research Management and Program Services. (Public Health Service Title IV, Part C)

1975			1976	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
69	$3,217,000	Indefinite	69	$3,081,000

Purpose: This activity funds: (1) the Director and his immediate staff concerned with administrative management, scientific and health reporting, financial management, program planning and evaluation, and computer processing services, (2) the scientific and administrative staff responsible for grant and contract programming, review and administration.

Explanation: The Institute Director and his immediate staff are responsible for providing leadership in the field of dental research and related higher education and providing leadership in scientific investigations and manpower training.

Accomplishments in 1975: The staff supported by this activity continued to provide administrative management, scientific and health reporting, financial management, program guidance and supportive services to the Institute's staff, in the furtherance of the Institute's overall research activities.

Objectives for 1976: Research management and program services will continue to provide for the overall administration, direction, and coordination of the Institute's programs.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$43,536,000	$7,924,000
Total obligations	43,536,000	7,924,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Caries	34	$8,140,000	34	$2,078,000
Periodontal and Soft Tissue Diseases		7,060,000		940,000
Restorative Materials		2,245,000		458,000
Craniofacial Anomalies		6,098,000		1,423,000
Pain Control and Behavioral Studies		1,500,000		32,000
Dental Research Institutes		7,200,000		—
Intramural Laboratory and Clinical Research	165	8,212,000	165	2,204,000
Research Management and Program Services	69	3,081,000	69	789,000
Total obligations	268	43,535,000	268	7,924,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions.....	268	268
Full-time equivalent of all other positions.	41	41
Average number of all employees.....	312	77
Personnel compensation:		
Permanent positions.....	$5,655,000	$1,414,000
Positions other than permanent.....	585,000	146,000
Other personnel compensation.....	48,000	12,000
Total personnel compensation.....	6,288,000	1,572,000
Personnel benefits.....	938,000	469,000
Travel and transportation of persons.....	226,000	57,000
Transportation of things.....	30,000	15,000
Rent, communications & utilitites.....	196,000	49,000
Printing and reproduction.....	67,000	17,000
Other services:		
Project contracts.....	4,575,000	815,000
NIH management fund.....	2,429,000	607,000
Other.....	986,000	268,000
Supplies and materials.....	878,000	220,000
Equipment.....	522,000	25,000
Grants, subsidies & contributions.....	26,405,000	3,811,000
Deduct quarters and subsistence charges.....	-4,000	-1,000
Total obligations by objects.....	43,536,000	7,924,000

Interim Period

Narrative

Funds needed for the interim period are based approximately on monies required as if this period were another quarter in the budget cycle. Included are funds for research and training grants and contracts with September 1 starting dates. ½

Direct operating estimates were based on approximately 25% of the 1976 level in all object classifications except personnel benefits (because of payment of continuation pay), travel, and equipment.

Caries--Research will be supported in this highly organized research and development effort in order to develop methods to eliminate caries as a major health problem.

Periodontal and Soft Tissue Diseases--Research will be supported in this program area to develop new knowledge which may lead to the prevention and eradication of these diseases.

Restorative Materials--Research will be supported to foster the development of new materials and methods for better treatment and prevention of dental and oro-facial disorders and diseases.

Craniofacial Anomalies--Research will be supported to develop information related to the etiology, pathology, prevention, and treatment of craniofacial malformations.

Pain Control and Behavioral Studies--Research will be supported to increase knowledge concerning the nature, etiology, pathophysiology, diagnosis and treatment of oral-facial pain, and to achieve greater utilization of behavioral sciences knowledge in the prevention and treatment of oral-facial diseases and disorders.

Intramural Laboratory and Clinical Research--Studies supported are concerned with the causes, treatment, control, and prevention of diseases and disorders of the oral cavity and facial region, e.g., dental caries, periodontal disease, oral-facial birth defects, and oral soft tissue diseases.

Research Management and Program Services--Funds will support (1) the Director and his immediate staff concerned with administrative management, scientific and health reporting, financial management, program planning and evaluation, and computer processing services, (2) the scientific and administrative staff responsible for grant and contract programming, review and administration.

FRIDAY, APRIL 12, 1975.

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES

WITNESSES

DR. G. DONALD WHEDON, DIRECTOR
DR. RONALD LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. BENJAMIN T. BURTON, ASSOCIATE DIRECTOR FOR PROGRAM ANALYSIS AND SCIENTIFIC COMMUNICATION, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
F. L. MILLS, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
DONALD F. CYPHERS, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER
DR. GEORGE BROOKS, ASSOCIATE DIRECTOR FOR EXTRAMURAL PROGRAM ACTIVITIES
DR. HAROLD ROTH, ASSOCIATE DIRECTOR FOR DIGESTIVE DISEASES AND NUTRITION
DR. NANCY B. CUMMINGS, ASSOCIATE DIRECTOR FOR KIDNEY, UROLOGIC AND BLOOD DISEASES

Mr. FLOOD. We now have the National Institute of Arthritis, Metabolism and Digestive Diseases. Welcome, Dr. Whedon, who do you have with you?

Dr. WHEDON. As usual, I have Dr. Benjamin Burton with me, Associate Director for Program Analysis and Scientific Communication, National Institute of Arthritis, Metabolism, and Digestive Diseases; and I have brought with me three new members of my staff because of the very responsible positions which they hold. I would like to introduce them to you. First, Dr. George Brooks, our new Associate Director for Extramural Program Activities; Dr. Harold Roth, new Associate Director for Digestive Diseases and Nutrition; and Dr. Nancy B. Cummings, new Associate Director for Kidney, Urologic and Blood Diseases; seated at the table with me are: F. L. Mills, Executive Officer, National Institute of Arthritis, Metabolism, and Digestive Diseases; and Donald F. Cyphers, Financial Management Officer, National Institute of Arthritis, Metabolism, and Digestive Diseases.

Mr. FLOOD. I think we should have a biographical sketch of the new people.

[The biographical sketches follow:]

BIOGRAPHICAL SKETCHES

Name: Dr. G. Donald Whedon.

Position: Director, National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD).

Birthplace and date: Geneva, N.Y., July 4, 1915.

Education: A.B., 1936, Hobart College; M.D. 1941, University of Rochester School of Medicine; Sc.D. (hon.), 1967, Hobart College.

Experience: Director, NIAMDD, 1962-present; Assistant Director, NIAMDD 1956–1962; Chief, Metabolic Diseases Branch, NIAMDD, NIH, 1952–1965; Physician, Outpatient Dept., New York Hospital, 1947–1952; Assistant Physician, Outpatient Dept., New York Hospital, 1944–1947; Assistant Professor of Medicine, Cornell University Medical College, 1950–1952; Instructor of Medicine, Cornell University Medical College, 1944–1950; Assistant in Medicine, University of Rochester School of Medicine and Assistant Resident Physician in Medicine, Strong Memorial Hospital, 1942–1944; Interne in Medicine, Mary Imogene Bassett Hospital, Cooperstown, N.Y., 1941–1942.

Association memberships: Association of American Physicians; the Endocrine Society (postgraduate committee, 1962–1965); American Rheumatism Association; American Diabetes Association (board of directors, 1970–73, postgraduate education committee 1971); American Federation for Clinical Research; New York Academy of Sciences; American Association for the Advancement of Science; American Medical Association; American Physiological Society; the Gerontological Society; American Institute of Nutrition; Pan American Medical Association; American Gastroenterological Association; Aerospace Medical Association; Council, National Program for Dermatology 1971–present.

Special Awards, Citations, or Publications: PHS Superior Service Award 1967; Citation to Alumni, University of Rochester, 1971; NASA Exceptional Scientific Achievement Medal, 1974; Certified, American Board of Internal Medicine, 1950; Certified, American Board of Nutrition, 1968; assisted DGMS in organizing program of multicategorical Clinical Research Centers in leading American medical institutions, 1959–61; Subcommittee on Calcium, Committee on Dietary Allowances, Food and Nutrition Board, National Research Council, 1959–64; Editorial Board, Journal of Clinical Endocrinology and Metabolism, 1960–67; Editorial Board, Calcified Tissue Research, 1967–present; Scientific Council of the Maryland Academy of Sciences, March 1965–71; principal investigator of Calcium-Nitrogen Metabolic Balance Study on NASA Gemini-VII Space Flight, December, 1965, and for similar studies on Skylab series of NASA space flights, 1973–74. Consultant to Space Medicine Division, Office of Manned Space Flight, NASA, Nov. 1963–74; University of Rochester University Alumni Council and Medical Alumni Association Council, 1971–present; University of Rochester Trustees Council, 1971–present, chairman, 1974–75. Chairman, Life Sciences Committee, NASA, 1974–present; member, Space Program Advisory Council, NASA, 1974–present.

Dr. Whedon is the author of over 50 scientific papers on metabolic and physiologic studies of convalescence, immobilization, paralytic poliomyelitis, diseases of bone particularly including osteoporosis, human energy metabolism, and space medicine.

Name: Dr. George T. Brooks.

Position: Associate Director for Extramural Program Activities, National Institute of Arthritis, Metabolism, and Digestive Diseases.

Birthplace and date: Okmulgee, Okla.; January 22, 1922.

Education: B.A., University of Kansas, 1945; M.A., University of Kansas, 1947; Ph.D., University of Kansas, 1949.

1971–74: Associate Director for Extramural Programs, National Eye Institute, National Institute of Health.

1969–71: Deputy Director, Division of Research Grants, National Institutes of Health.

1966–69: Chief, Latin American Office, National Institutes of Health.

1965–66: Hematology Program Director, Extramural Programs, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

1963–65: Training Consultant, National Institute of Child Health and Human Development, National Institutes of Health.

1962–63: Grants Associate, U.S. Public Health Service, National Institutes of Health.

1951–1962: U.S. Government foreign assignments.

Association memberships: Sigma XI; Phi Sigma, Entomological Society of America; AAAS.

Harold P. Roth, M.D.

Date and place of birth: August 2, 1915, Cleveland, Ohio.

Degrees: Western Reserve University, Cleveland, Ohio, 1936, B.A.; Western Reserve University, Cleveland, Ohio, 1939, M.D.; Harvard University, Boston, Mass. M.S. in hygiene, biostatistics, and epidemiology, 1967.

Internship: Cincinnati General Hospital, Cincinnati, Ohio, rotating internship, July 1940; Boston City Hospital, Boston, Mass, house officer, 5th medical service, September 1940 to July 1942.

Residency: Assistant resident in medicine, Barnes Hospital, St. Louis, Mo., July 1942 to July 1943.

Postgraduate training: Harvard Medical School (endoscopy), February–April, 1948.

Past professional appointments: Assistant physician, Department of Medicine, Washington University, 1942–43; clinical instructor, Department of Medicine, Western Reserve University, 1949–52; senior clinical instructor, Department of Medicine, Western Reserve University, 1953–55; assistant professor, Department of Medicine, Western Reserve University, 1955–63; assistant physician, Department of Medicine, University Hospitals, 1957——.

Current professional appointments: chief, gastroenterology service, Veterans Administration Hospital Cleveland, Ohio, 1947——; director, gastroenterology training program, University Hospitals and V.A. Hospital, 1963——; associate professor, Department of Medicine, Western Reserve University, 1963; associate professor, Department of Community Health, Case Western Reserve University, 1971– ; associate physician, University Hospitals 1969– ; consultant-assistant physician, Department of Medicine, Highland View Hospital; visiting physician in gastroenterology, Department of Medicine, Cleveland Metropolitan General Hospital, 1973– ; associate director for digestive diseases and nutrition, NIAMDD, NIH, Bethesda, Md., 1974– .

Medical societies: American Gastroenterological Association, associate, 1957–60, member, 1960– , epidemiology committee, research, education committee; American Association for the Study of Liver Disease, 1957– ; Midwest Gut Club, 1966– ; Central Society for Clinical Research, member, 1960– ; American College of Physicians, associate, 1946–55, fellow, 1955– ; Cleveland Academy of Medicine.

Honors and fellowships: Phi Beta Kappa; special fellow, U.S.P.H.S., Harvard School of Public Health, 1966–67.

Certification: American Board of Internal Medicine, 1946; subspecialty gastroenterology, 1956.

Military service: August 1943–46. Chief of the General Medical and Cardiovascular Renal Section, 40th General Hospital—ETO; Commanding Officer, 11th Medical General Dispensary—Pacific Theatre.

Marital status: Married, two children, Anita A., born January 18, 1958; Edward Harris, born August 22, 1962.

Home address: 10319 Gary Road, Potomac, Md. 20854.

Nancy Boucot Cummings, 2811 35th Street, NW., Washington, D.C. 20007.

Birthplace: Philadelphia, Pa., date: February 21, 1927.

Husband: Milton Curtis Cummings, Jr. Children: 3.

Education: B.A. February 1947, Oberlin College, Oberlin, Ohio; February–June 1947, Graduate School, Radcliffe College, Cambridge, Mass., history, no degree; M.D. June 1951, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Licenses: diplomate of National Board of Medical Examiners (1952); licensed to practice medicine in: District of Columbia, Massachusetts, Pennsylvania.

Career: June 30, 1951 to June 30, 1952—rotating internship, Pennsylvania Hospital, Philadelphia, Pa.

July 1, 1952 to June 30, 1954—residency, internal medicine, Hospital of University of Pennsylvania, Philadelphia, Pa.

July 14, 1954 to June 15, 1955—research and clinical assistant, medical professorial unit, Royal Hospital of St. Bartholomew, London ECI, England. (Prof. Ronald V. Christie).

June 15, 1955 to August 1, 1955—Research and Clinical Assistant, Medical Professorial Unit, Manchester Royal Infirmary, Manchester, England. (Prof. Robert Platt).

Sept. 4, 1955 to June 30, 1958—Research Fellow, Harvard Medical School; Assistant in Medicine, Peter Bent Brigham Hospital, Boston, Mass. (Renal Laboratory, Chief, John P. Merrill).

July 1, 1958 to August 30, 1959—Research Fellow, Dept. of Biochemistry, Harvard Medical School, Boston, Mass.

Sept. 1959 to August 1962—Guest Worker, Laboratory of Intermediary Metabolism, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md. (Dewitt Stetten, Jr., M.D., Ph. D.)

Sept. 4, 1962 to March 1966—Research Medical Officer, Dept. of Surgical Physiology, Walter Reed Army Institute of Research, Washington, D.C. (Paul E. Teschan, M.D.).

March 21, 1966 to March 1972—research medical officer, Experimental Medicine Division, U.S. Naval Medical Research Institute, Bethesda, Md. (Paul D. Doolan, M.D.)

1966 to March 1972—consultant in nephrology, Department of Medicine, Naval Hospital, Bethesda, Md.

1960 to 1970—clinical instructor of medicine, Georgetown University School of Medicine, Washington, D.C.

1970 to present—clinical assistant professor of medicine, Georgetown University School of Medicine, Washington, D.C.

1972 (March) to Oct. 1973—program officer, Kidney Disease Collaborative Program, NIAMDD, NIH, Bethesda, Md.

October 1973 to October 1974—special assistant to the director, NIAMDD for Renal and Urologic Diseases.

November 1974 to March 1975—associate director, acting, for kidney, urologic, and blood diseases, NIAMDD.

March 1975—associate director, kidney, urologic, and blood diseases, NIAMDD.

Fellowships: (honors) Adelia Field Johnston Fellowship from Oberlin College, 1948; 1954–55—National Foundation for Infantile Paralysis, research fellowship; 1955–57—American Heart Association, research fellowship; 1957–62—American Heart Association, advanced research fellowship; 1969—ASN travel grant to attend International Congress of Nephrology, Stockholm; 1972—ASN travel grant to attend International Congress of Nephrology, Mexico City.

Field of interest: General—internal medicine; specific—nephrology, physiology, biochemistry.

Societies/committees: American Society of Nephrology; International Society of Nephrology; American Society of Pediatric Nephrology; American Society for Artificial Internal Organs; Southern Salt, Water, and Kidney Club; American Federation for Clinical Research; Biophysical Society; American Association for Advancement of Science; European Dialysis and Transplant Association.

Medical Advisory Board, National Kidney Foundation, D.C. Chapter, 1969 to present.

Professional Advisory Board, Kidney Foundation, D.C. Chapter, January 1975 to present.

Chairman, 8th Kidney Symposium, National Kidney Foundation, D.C. Chapter, February 23, 1972.

Research Committee, Washington Heart Association, 1969 to present.

1967–72—Interagency Board of U.S. Civil Service Examiners (panel member).

1970—member, technical assistance committee, Metropolitan Washington Regional Medical Program, for a regional nephrology program.

1970–72—seminar committee, Naval Medical Research Institute; chairman, 1971–72 (March).

1971–72—consultant, artificial kidney-chronic uremia program, National Institute of Arthritis and Metabolic Diseases.

1972 to present—fellow, College of Physicians of Philadelphia.

1973 to present—Council on Kidney, American Heart Association.

1973 to present—Scientific Advisory Board, National Kidney Foundation.

1973 to present—cochairman, National Kidney Foundation Advisory Committee on Epidemiology and Statistics of Kidney Disease.

1974 to present—coeditor, Fogarty International Center Monograph on Prevention of Kidney and Urinary Tract Diseases.

1975 to present—coeditor, Symposium Issue, Epidemiology of Kidney Disease—J. Chronic Diseases.

Mr. FLOOD. At our meetings here, any time anyone wants to sound off about some questions, just go ahead. The important think is to have you here to participate. You go ahead and speak up if it is important.

You have a prepared statement. How would you like to handle it?

Dr. WHEDON. I would like to read the statement.

Mr. Chairman and members of the committee, it is an honor and a welcome opportunity for me to appear before you once again. This year, we are especially mindful of many new responsibilities facing this Institute, following passage of the National Diabetes Mellitus Research and Education Act, and the National Arthritis Act, with their provisions calling for increased and broadened efforts in these two important disease fields. We are also this year undertaking a number of other special initiatives, such as the U.S.-U.S.S.R. Cooperative Arthritis Program, in which we are undertaking several joint research efforts in arthritis and allied conditions with investigators in the Soviet Union.

U.S.-U.S.S.R. COOPERATIVE ARTHRITIS PROGRAM

Mr. FLOOD. Is there anything geographically or because of any other reasons which makes this especially of concern to the Soviets?

Dr. WHEDON. The Soviet Union has had a long interest in bone and joint diseases. Dr. Lamont-Havers, when he was with our Institute, really initiated the contact with the Russians and went to the Soviet Union last year as a part of the beginning of this program.

Dr. LAMONT-HAVERS. I think the Soviets recognize this as a major health problem within the Soviet Union. They have done some studies on geographic distribution but we did not know about it until last year. I think they will be of interest to us once we get more data on them.

Mr. FLOOD. They have such a wide, divergent ethnic stock.

Dr. LAMONT-HAVERS. Also tremendous variety in temperature and climate and also a relatively stable population, which we do not.

Mr. FLOOD. What does that mean?

Dr. LAMONT-HAVERS. Our population moves.

Dr. WHEDON. As you know, this Institute has the widest span of categorical disease responsibilities. In addition to our research support in arthritis and other connective tissue diseases, and diabetes and other meabolic disorders, we are responsible for research in digestive diseases and nutrition, diseases of the kidney and urinary tract, diseases of the blood, bones, and skin.

SPECIAL REPORTS

I should like to point out some particular aspects of our programs and of progress therein which should indicate how we are meeting the challenge of our diverse and serious disease problems. In order to present a more detailed description than is possible in this brief presentation, we have prepared several special reports which I am submitting herewith to the committee.

Mr. FLOOD. Thank you very much, that is a good idea.

[The reports follow:]

ARTHRITIS, RHEUMATIC DISEASES, AND RELATED DISORDERS

The arthritic diseases, rheumatism, and related bone and connective tissue disorders afflict more than 18 million people in the United States, at a cost of about $4 billion to the nation annually. The most prevalent form of arthritis is degenerative joint disease, known as osteoarthritis; more than half of all people beyond the age of 55 exhibit such degeneration. The most severely crippling form of rheumatic disease in younger age groups is rheumatoid arthritis, which afflicts about 5 million Americans. Each year, however, important steps are taking place in understanding and controlling these diseases, largely as a result of extensive biomedical investigations, both at basic and applied levels of research, conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Obligations for Programs in Arthritis

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases	$14,374,000	13,808,000	17,116,000*	13,171,000	13,921,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Arthritis, the oldest known chronic disease, remains today the most prevalent crippler in the United States. About a hundred distinct disorders are represented in the classification "arthritis and rheumatism," of which more than a dozen are considered serious public health problems, notably rheumatoid arthritis, juvenile rheumatoid arthritis, degenerative joint diseases, systemic lupus erythematosus, and gout.

These diseases result in unemployment equivalent to the loss of about half-a-million people in the United States each year. The government will spend more than a billion dollars in disability payments to individuals crippled by arthritis during this decade. The estimated overall cost to individuals and government has been placed at $4 billion yearly.

Research continues to improve treatment of arthritis. Substantial progress is being made in the areas of basic research in the fundamental disciplines which enhance understanding of rheumatic disorders. Investigators and grantees of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) are developing basic information to elucidate problems of inflammation and tissue destruction characteristic of these diseases and the immunologic mechanisms that, in some instances at least, initiate and perpetuate these processes.

* Includes $3,040,000 in 1974 from the release of 1973 impounded funds.

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RHEUMATOID ARTHRITIS

This form of arthritis afflicts about 5 million people in the United States. Although investigation has provided more effective ways of limiting the associated pain and deformity, the cause of this crippling disease remains obscure. An important guide in the continuing search comes from recognition that the underlying abnormality is not limited to joints but may affect any organ of the body. For example, NIH grantee Dr. Robert Turner and associates at the Bowman Gray School of Medicine at Winston-Salem, North Carolina, have added to knowledge of cardiac involvement in this disease, making use of echocardiography, a method of reflecting ultrasonic sound from heart structures.

The mechanism at work in causing this widespread chronic inflammation involving various systems of the body is believed by many investigators to be an abnormal reaction of the body's immune system, a reaction stimulated by infection or a misdirected attack by the body's defense systems on its own tissue (an autoimmune reaction). A mechanism of this kind, with varied trigger factors, agrees well with what is known of the natural history of this disease. Although a number of infectious agents have been isolated from tissues of patients with rheumatoid arthritis, none has been identified as a definite cause of the disease.

A novel approach to this important line of inquiry has been taken by Institute grantees, Dr. Norman L. Gottlieb and associates at the University of Miami School of Medicine. They conducted an epidemiologic survey of pet ownership (dogs, cats, and birds) in patients with rheumatoid arthritis. Using groups of patients with other forms of arthritis and non-arthritic disease for comparison and directing their inquiry to the five year period preceding the onset of arthritis, these investigators found in the rheumatoid arthritis group a significantly higher prevalence of pet ownership. Although these findings seem to lend support to the hypothesis of an infectious causative factor in rheumatoid arthritis, the limited size of the study and the need to consider alternate explanations such as hypersensitivity to fur or feathers, are factors to be considered in interpreting the results. Additional research appears warrented since it is known that pets harbor a wide variety of infectious organisms which are known to produce human disease.

Mechanisms of Immunity Under Investigation

Numerous studies have demonstrated an approximate correlation between the severity of rheumatoid arthritis and the presence of rheumatoid factor in the blood. In some patients with rheumatoid arthritis, however, this factor is lacking, making diagnosis and classification more difficult. Now, recent studies pointing to the involvement of the complement system, a major link in the body's immunological responses, have been shown to be of value in this respect particularly in those patients who are serologically negative for rheumatoid factor.

Determination of complement in fluid recovered from inflamed joints has been shown to be helpful in evaluating rheumatoid arthritis patients. In recent studies, Dr. Frederic C. McDuffie and his associates at the Mayo Clinic, Rochester, Minnesota, were able to identify four groups from among 62 patients with rheumatoid arthritis on the basis of the presence or absence of serum rheumatoid factor and low or normal joint fluid complement levels. The relationship between joint fluid complement levels and the severity of rheumatoid arthritis was studied by comparing clinical, laboratory and X-ray tests with results of similar measurements in control patients. This has added to our knowledge in two ways, first, by showing that joint fluid complement determination can be used to diagnose and classify patients with arthritis, particularly in the absence of rheumatoid factor in the blood, and second, the finding of low complement levels in joint fluid is consistent with the hypothesis that immunologic factors--specifically an antigen-antibody reaction within the joint that utilizes complement--play an important part in the development of rheumatoid arthritis.

An Institute grantee at the University of California, San Diego, Dr. Nathan J. Zvaifler, has conducted research which demonstrates that the complement sequence--a series of events in which a group of blood proteins interact to initiate inflammation--contributes significantly to the progressive destruction of joints that is characteristic of rheumatoid arthritis. He concludes from his studies that antigen-antibody complexes are responsible for activation of the complement sequence.

In addition to the work on proteins active in immune reactions, important evidence for operation of immune mechanisms in these diseases comes from study of the immune cells.

Of great importance to establishing a link between immune mechanisms and rheumatoid diseases is the finding by Dr. Paul Terasaki and associates at UCLA that most patients with ankylosing spondylitis possess a common genetic cellular factor (histocompatability antigen) present in only a small percent of the general population. The association of the disease with such a factor suggests that some aberrant, genetically controlled, cellular immune response may be the cause. Such factors first came under study in the search for tests of compatibility between donor and recipient in the transplantation of organs like the kidney. The finding of an association between compatibility factors and disease is a good illustration of how unpredictable the path of discovery can be.

Cells known as B-lymphocytes play an important role in the inflammatory reaction of tissue in individuals with rheumatoid arthritis. An Institute grantee, Dr. Morris Ziff of the University of Texas Southwestern Medical School, after observing large numbers of cells from rheumatoid arthritis joint membranes under the electron microscope, suggests that immune responses occur both in the joint fluid and in joint tissue. Such studies sustain the long-standing search for an infectious agent in rheumatoid arthritis. Institute scientists and grantees continue to search for viral agents associated with rheumatoid arthritis. Investigators have tested the susceptibility of cells taken from rheumatoid patients to numerous viruses, but so far no concrete evidence has been found demonstrating a viral trigger.

Treatment of Rheumatoid Arthritis

The program of treatment in the early stages of rheumatoid arthritis is designed to relieve pain, to control inflammation and to prevent deformity. Many cases can be controlled satisfactorily on a program of rest and physiotherapy, utilizing salicylate drugs such as aspirin. In some cases, the disease subsides without intervention. In other cases, progressive joint damage may not be stopped or slowed down with rest and salicylates, or the process, having subsided, may flare up with any attempt to resume normal activity. The physician has available a wide range of alternative drugs which, although they may be more effective in controlling the disease are also more likely to have toxic side-effects. The list includes gold salts, corticosteroids, chloraquine, penicillamine, and the immunosuppressive agents. Because of the toxic effects of these drugs, those who administer them must follow strict guidelines exploring the safest therapy first, restricting use of the most hazardous to cases with life-threatening complications or potential for serious crippling. Meticulous follow-up with monitoring for toxic effects is mandatory. Continuing research in this area constitutes a major aim of both intramural and extramural programs of the Institute.

Research by Dr. Morris Ziff and Dr. Eric R. Hurd at the University of Texas Southwestern Medical School has confirmed the efficacy of the immunosuppressive drug cyclophosphamide in treating rheumatoid arthritis. They are investigating the mechanism of action as well. The investigators found that clinical improvement correlates well with reduction in numbers of monocytes and small-lymphocytes, in the blood of treated patients. This observation provides both a means of monitoring treatment and a clue to the mechanism of drug action.

Recently, an Institute grantee, Dr. John T. Sharp and associates of the Baylor College of Medicine showed by radiologic evaluation that gold therapy beneficially altered the course of rheumatoid arthritis in a group of patients given weekly gold injections for 22 weeks and maintenance injections at increasing intervals for two years. Periodic radiologic examination showed arrest of bone and cartilage destruction in several patients and a significant slowing of the progression rate of joint damage for the treated group.

Corticosteroid drugs, despite the dramatic relief they sometimes provide, do not alter the course of rheumatoid arthritis. Even small doses given for prolonged periods can result in serious clinical complications, e.g. bleeding from peptic ulcer or loss of calcium from bones. A recent study by Institute grantee Dr. Louis V. Avioli and his associates at the Washington University School of Medicine, St. Louis, has shown a similarity in the pattern of bone loss resulting from corticosteroid therapy with that observed in primary hyperparathyroidism. The researchers suggest that patients receiving chronic corticosteroid treatment may experience bone loss as a result of elevated parathyroid hormone levels. The increased level appears to be secondary to decreased intestinal calcium absorption. Preliminary studies indicate that the process can be reversed by administration of vitamin D which acts to increase intestinal calcium absorption.

In view of the problems created by administering drugs, great interest attaches to treatment based rather on removing a harmful agent. Surgical removal of the thickened connective tissue so conspicuous in diseased joints of the individual with rheumatoid arthritis - synovectomy - was first introduced as an aid in the treatment of advanced cases, but is now coming to be used in earlier stages of the disease. Studies conducted at the NIH Clinical Center and elsewhere confirm the finding of reduced inflammation and improved function; they suggest, too, that to remove the inflamed tissue is to remove the agent active in destruction of the joint.

Search for remedial agents and for understanding of the disease

Understanding of a disease process generally provides a valuable guide to the search for effective remedial agents. The limited understanding of rheumatoid arthritis, however, has meant that search for such agents must proceed largely through a trial and error process. Once successful agents are found, they become the focus of intense investigation, and understanding the mechanism by which a newly discovered treatment produces its effect hopefully leads to fresh perspectives on this elusive disease. Thus Drs. Stephen Malawista and Daniel Wright, Institute grantees at Yale University report that the anti-inflammatory effects of colchicine, long recognized as very effective in relief of the acute arthritis of gout, acts by preventing release of destructive enzymes from white blood cells. Release of these enzymes, normally stored as intracellular particles or "lysosomes," may well be the final common path in production of cartilage destruction and connective tissue overgrowth. This inquiry into the cellular response to colchicine thus establishes a valuable link between old, well-tested knowledge of treatment and understanding of disease mechanisms provided by new knowledge of cellular metabolism.

Another empirical approach to treatment now being examined from the perspective of new knowledge is that of aiming for prompt control of inflammation. A fresh vantage point is being provided by the observations of Dr. Edward D. Harris, Jr., Institute grantee at Dartmouth University, on variation in collagen destruction with temperature. He found the enzymatic destruction of collagen fibrils, one of the key structural components of joints, proceeds at a much faster rate at the elevated temperature characteristic of inflammation (34-37.6°C). Collagen breakdown was as much as four times greater than at temperatures characteristic of normal joints (30.5-33°C).

This finding raises questions concerning treatment of inflammed joints with induced heat (such as diathermy). Such treatment may increase internal joint temperatures and may actually aggravate the inflammation and joint damage through stimulation of collagen destruction. Dr. Harris' work suggests that part of the benefit from anti-inflammatory therapy in rheumatoid arthritis may be secondary to lowering the internal temperature of the affected joints, thereby decreasing the rate at which collagenase degrades cartilage collagen. His finding provides one explanation of the mechanism of effective local suppression of joint inflammation by intra-articular injection of steroid drugs.

This new insight into the mechanism of tissue destruction comes as a direct outgrowth of research on the change from tadpole to frog where Drs. Jerome Gross and Charles Lapiere demonstrated that a collagen-destroying enzyme had a role in dissolution of the tadpole's tail. Working with Dr. Gross, Dr. Stephen Krane succeeded in demonstrating the presence of such an enzyme in human tissues and the destructive effects of this enzyme on joint structures. It was then, in collaboration with Dr. Krane, that Dr. Harris embarked on the study of temperature dependence of the destructive effects. The sequence from tadpoles to temperature effects has been supported by a combination of research, training and Research Career Development awards extending over more than a decade.

Arthritis with deformity as seen in children presents features that mark it as a separate disease, particularly when high fever and skin eruption are present without the elevation of rheumatoid factor so characteristic of adult rheumatoid disease. The observations of Dr. Paul Terasaki on the prevalence of a genetically determined cellular factor (histocompatibility antigen W27) in both adult and juvenile forms of arthritis have, however, demonstrated a link between them. Such evidence suggests that there is a common origin to various arthritic diseases, such as inherited susceptibility to infectious agents which are yet to be identified.

OTHER CONNECTIVE TISSUE DISORDERS

Systemic Lupus Erythematosus

Another connective tissue disorder in which the Institute supports research is systemic lupus erythematosus (SLE), a chronic inflammatory disease of unknown origin which may affect several organs, the joints, lung, spleen, heart or kidney. It affects some 50,000 new victims each year, particularly women between 20 and 40 years of age. Considerable evidence indicates that SLE, too, may be a disorder of the immune mechanisms of the body, and that it may be triggered by an infectious process although sometimes the disease appears as a reaction to certain drugs. Investigators at the NIH Clinical Center in Bethesda are, therefore, studying the effects of the immunosuppressive agents cyclophosphamide and azathioprine in efforts to control the immune system and thereby the disease process.

Institute grantee Dr. Frederic C. McDuffie and associates at the Mayo Clinic have reported for the first time involvement of immune complexes and complement in the onset of pericarditis in association with SLE. The investigators believe that measurement of complement in pericardial fluids may be helpful in diagnosis of certain pericardial conditions, SLE, and other diseases involving an immune-complex mechanism.

Osteoarthritis

Osteoarthritis (degenerative joint disease) is a common, severe disability that appears to be the result of the erosion and disorganization of joint tissues that generally accompany the aging process. Within the heterogeneous category of degenerative arthritis, different

factors can be recognized as being responsible for the accelerated deterioration. These include the unusual wear experienced by those with deformity or obesity and early degenerative changes with a strong familial history of occurring at such specific sites as the terminal finger joints or the hip. Efforts in preventing unusual wear are critical where deformity or obesity is involved and for early degeneration of genetic origin new developments in joint replacement, as described under Orthopedics, now enable many to return from wheelchair existence to an active life.

Gouty Arthritis

More than a half million Americans, nearly all of them men, have gout, a hereditary disorder of purine metabolism. In this disorder, uric acid, a breakdown product of purines, themselves products of protein metabolism, is deposited under the skin or in and around the joints in the form of the salt, sodium urate. These salt crystals may cause excruciating pain and if treatment is not initiated, the deposits will grow. Eventually these deposits may form distinct masses which bring about permanent destruction of the joints and crippling. Uric acid stones may form in the urinary passages and lead to impairment of kidney function.

Of the common joint disorders, gout responds most favorably to treatment. Past research, to a large extent conducted and supported by the Institute, led to elucidation of the basic mechanisms of the disease and to study of new drugs, such as allopurinal, which counteract uric acid synthesis and buildup in the body, and other drugs which stimulate renal excretion of uric acid. Institute investigators are pursuing a number of leads relates to the underlying cause of gout and the manner by which typical gouty inflammation is produced.

BONE DISEASES AND ORTHOPEDIC RESEARCH

The Institute mission in bone disease is served by several Institute programs, notably, connective tissue metabolism (in the arthritis program) as it related to bone matrix, tendons, ligaments, and wound healing, and calcium metabolism, including investigation of nutritional factors and endocrine regulation in the supply and distribution of this critical element. A growing contribution to the Institute's mission in diseases of bones and joints comes from investigations originating with concerns of the orthopedic surgeon. Recent developments in development of artificial joints provide an instructive example of this contribution.

Development of specific artificial joints - shoulder, elbow, finger, hip and knee - and methods for attachment of these joints to bones, tendons, or muscles is a major interest of orthopedics research. Successful transplants at natural joints are dependent upon a better understanding of the graft-rejection process, bone immunology, bone metabolism, fracture healing, skeletal attachment, skeletal-soft tissue trauma, and other factors in the healing process. Research in these areas in under way. Many of these efforts involving connective tissues and cartilage are directed toward a better understanding of biochemical structure, ultrastructure, genetic factors, and enzymology of these tissues, as well as to the process of tissue-skeletal repair.

Interest in implantable materials has brought a recent influx of engineers and polymer and ceramic chemists into biomedical research.

Studies are under way to determine the best materials for fabrication of joints that will display minimal antigenicity and toxicity, maximum acceptance by the body and will also exhibit little wear or corrosion. Materials with these characteristics will enable the joint to remain securely attached to the skeletal or muscular system and will not necessitate replacement throughout the lifetime of the patient.

Total Replacement of the Hip

Hip joint replacement has proven to be one of the most successful orthopedic procedures in restoring mobility, even in many cases where previous reconstructive surgery has failed. The Institute provides grant support to several researchers performing and evaluating total hip replacement at centers throughout the United States.

The artificial hip is probably the most advanced of the artificial joints under study. Imperfections still exist in the materials used to fabricate the joint and in methods of attachment. Researchers are presently working with carbon reinforced plastics and ceramics, TRIP steel (which is an alloy of steel, chromium, and nickel), and other metals. Porous metals and metals coated with porous ceramics or plastics are being used in an effort to obtain implant attachment through ingrowth of tissue into the pores of the implant. Many of the materials now in use promise adequate durability for most older patients. Surgeons suspect, however, that the plastic socket now used may eventually have to be replaced in patients who received their implant when younger. The outlook for replacement of joints of all kinds in the treatment of arthritic conditions is rapidly improving. Within the next few years, it is expected that prostheses with increased wear characteristics and cements which are more compatible with human bones will be developed.

Bone Research

NIAMDD grantee Dr. Ali Seireg at the University of Wisconsin is conducting research on the effects of stress on bone mineral content, the role of muscle fatigue in fracture, and the cause of wear in joints. By analyzing the bones of rats subjected to an exercise program, Dr. Seireg has found that frequency and magnitude of stress applied to the leg changes bone size and mineral content and, therefore strength. While stress and exercise lead to increased bone strength, excessive exercise also leads to damage in the joints. Like bone, cartilage increases in mineral content when it is under stress. Dr. Seireg has found that as exercise calcifies the cartilage, the joint stiffens and the stress distribution becomes uneven, making the cartilage corrode more rapidly. Degradation of synovial fluid, the lubricant in joints, also causes cartilage to become worn. The investigator has found that the body cannot rejuvenate synovial fluid quickly enough when exercise is too great. As the synovial fluid breaks down, the temperature in the joint rises. Joint temperature is thought to be useful as a tool for measuring damage in joints, and is one of several techniques researchers have developed for testing drugs and treatment methods for arthritis caused by excessive stress.

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OUTLOOK

The studies mentioned here are included in the 150 ongoing research efforts supported by grants or conducted in the NIH laboratories in Bethesda in the area of arthritis, rheumatic diseases, and related disorders. This research is illustrative of the Institute's commitment and of recent progress. This continuing effort is constantly improving treatment, understanding and control of these diseases, while increasing the foundation of basic scientific knowledge which could lead to an eventual cure or prevention of these disorders.

COOLEY'S ANEMIA

The study of the processes and functions of blood cells and other constituents is essential to provide insight into the genetic basis of inherited blood disorders such as Cooley's anemia. It is estimated that there are more than 1,000,000 persons in the United States who suffer from disabling or killing disorders of the blood, including the anemias and bleeding disorders.

A recent national survey of physicians showed that at least 2,400 patients with Cooley's anemia are being maintained with the aid of chronic transfusion therapy. Worldwide, the problem is of greater scope with the thalassemias being the most common inherited single gene defect. On Cyprus, for example, 1 in 200 inhabitants has Cooley's anemia, and 15 percent of the population carries the trait. Where blood transfusion is not readily available, life expectancy for those afflicted seldom exceeds 2 to 4 years.

Obligations for Programs in Cooley's Anemia

	1973	1974	1975 Estimate	1976 Estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases				
Cooley's anemia	$ 992,000	$1,224,000*	$1,158,000	$1,208,000
National Heart and Lung Institute:				
Cooley's anemia	$1,121,000	$1,206,000	$1,325,000	$1,325,000
Total	$2,113,000	$2,430,000	$2,483,000	$2,533,000

National Institutes of Health
National Institute of Arthritis, Metabolism, and Digestive Diseases

A steady advance has been made in our knowledge of Cooley's anemia, (also known as Thalassemia Major and Minor, Mediterranean anemia, Hereditary Leptocytosis, and Familial Microcytic anemia) much of it during the past decade. Diagnostic techniques in the blood diseases have become more precise, and prompt and accurate diagnosis is frequently the key to initiating treatment that extends life. Institute-supported research has contributed much to knowledge of the molecular structure of hemoglobin, the key substance in red blood cells which carries oxygen from lungs to tissues, and of the disordered sequence of amino acid building blocks in abnormal hemoglobins.

Through research in its Bethesda laboratories and clinics, and through numerous grants to scientists at research centers across the country, the National Institute of Arthritis, Metabolism, and Digestive diseases (NIAMDD) is investigating many blood disorders, including Cooley's anemia. The National Heart and Lung Institute (NHLI) shares the responsibility for Cooley's anemia research with NIAMDD. Blood is such a

* Includes $119,000 in 1974 from restoration of 1973 impounded funds.

complex substance that any new discovery about it will open possibilities of biomedical investigation in related fields as well. For example, the development of a cell-free system for studying hemoglobin synthesis not only provides new information that may be applicable to the genetic control of this process, but can also serve as a prototype for the synthesis of other proteins in other tissues. This past year investigations have contributed many important research findings.

National Cooley's Anemia Control Act

New initiatives and investigations are forthcoming in the area of Cooley's anemia following passage of the National Cooley's Anemia Control Act, which provides for expanded programs of research, diagnosis, prevention and treatment of this disorder. The main responsibility for conducting research in Cooley's anemia rests with the NIAMDD. Under the provisions of the National Heart, Blood Vessel, Lung and Blood Act of 1972, however, a comprehensive national plan for the future research needs in Cooley's anemia will be included in the NHLI's report required under that Act.

Cooley's Anemia: The Disease

Cooley's anemia is an inherited blood disorder which occurs primarily in persons of Mediterranean ancestry. In the United States most of the victims are of Italian, Greek, Turkish, Southern French or North African descent, although the disease is not limited to these groups.

As in many genetic blood disorders, those who inherit the trait for the disease from only one parent will become "carriers" (who can pass on the trait to their own offspring) and are usually free of symptoms; those who inherit the gene from both parents have the overt disease. This severe form of the disease occurs, on the average, in one fourth of the children of parents who both carry the trait. Cooley's anemia is characterized by the production of abnormally thin red blood cells with abnormal mechanical fragility and by a profound anemia which appears soon after birth; severe effects include enlargement of its spleen and liver and grossly active bone marrow that may produce thickening of facial bones. The anemia is due to the inability of the bone marrow to synthesize a complete hemoglobin protein. This results in abnormal red cells that are then removed from the circulation by the spleen, reducing the overall number of red blood cells available for transport of oxygen from the lung to all body tissues.

No cure is known, and the only effective treatment is repeated administration of blood by transfusions, usually once a month but sometimes more frequently, to alleviate the constantly recurring anemia. A serious complication is a progressive overload of iron in the body resulting from frequent transfusions. Carriers generally enjoy normal health and life span. The prevalence is not really known but the best available estimate is that about 200,000 persons in this country carry the trait.

Diagnosis is relatively straightforward in those who have clinical disease, but definitive diagnosis in those who only carry the trait is much more difficult and requires relatively sophisticated hematologic tests.

Inter-Institute Coordinating Committee

The National Institutes of Health has formed an Inter-Institute Committee on Cooley's anemia in order to assure that the research efforts related to the disease are coordinated into an effective total effort.

A top priority program in relation to the Cooley's Anemia Control Act is the search for a more effective chelating agent for removal of the undesirable iron stores resulting from repeated blood transfusions to patients. Several research contracts for development of such an agent have been let and funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases during Fiscal Year 1974.

The contractors, together with other experts from across the country, attended a workshop at NIH in September, 1974, to coordinate their activities. The investigators foresee the development of a safe and effective chelating agent.

Iron Chelating Agent

Clinical trials will attempt to determine the usefulness of drugs designed to increase excretion of excess iron from the body. Known iron chelators do increase iron excretion, but their value in improving health and preventing the complications of iron overload has not been determined. Efforts are under way to evaluate a wide range of compounds for safety and effectiveness in preventing damage from accumulations of this element. Promising compounds of microbial origin, as well as those synthesized in chemical laboratories, will be developed and evaluated first in animals for biological safety and effectiveness.

Over the next several months physicians from many cities will cooperate in designing trials. Patients with Cooley's anemia will be asked to participate in the studies.

Promising Animal Studies

The initiation of a pilot clinical trial to evaluate the compound 2,3-dihydroxybenzoic acid (2,3-DHB) is now underway by an NIAMDD grantee, Dr. Anthony Cerami, and associates, at the Rockefeller University in New York. They have reported promising animal studies with the compound which will now be evaluated in the treatment of patients with iron-overload resulting from transfusions. The compound, which can be administered orally, removes iron from an overloaded rat without affecting the excretion of other needed trace metals. Adverse toxic effects have not been observed to date in the animals. These studies, to be conducted in selected patients, are expected to establish whether this drug has a feasible therapeutic role in iron-overload in Cooley's anemia.

Using DF in Iron Removal

At the present time, only desferrioxamine (DF) is available generally in the U.S. for removing excess iron. The drawbacks to its use are two:

1) removal of iron by DF is demonstrated only after the body's iron stores have become saturated and the pathological accumulation has begun, which means it may not be effective in preventing iron overload, and, 2) it must be given daily by deep intramuscular injection. The NHIL will test DF in national cooperative clinical trials to determine if its use will materially benefit patients by preventing or slowing the pathological effects of excess iron.

Cooperative Clinical Trial

The National Heart and Lung Institute plans to conduct another study of importance in the Cooley's anemia program. This is a cooperative clinical trial to study transfusion therapy for children with Cooley's anemia. While frequent blood transfusions result in better growth and less liver, spleen and bone abnormalities, the long-term effects of additional iron accumulation due to the increased transfusions are a source of concern. Therefore, careful study is essential to determine the optimal number of blood transfusions.

Cooley's Anemia Screening Test

Now underway at the National Heart and Lung Institute is a pilot program of screening for thalassemia trait and counseling for those affected with the condition. The principal question to be answered is whether or not a mass screening program for Cooley's anemia should be considered for the country. A large scale screening program would require development of a simple, inexpensive screening test. Such a test is not available at present and has defied development thus far. The NHLI is also field testing a procedure which identifies possible both sickle cell anemia and Cooley's anemia carriers, using micro-chromatography techniques.

The Health Services Administration (HSA) of the Public Health Service also plans to fund a small service-oriented screening, counseling and education program in cooperation with the Cooley's Anemia Foundation. The HSA effort and the NIH pilot programs in screening will be coordinated to insure maximum benefit from the knowledge gained. The Health Services Administration plans to undertake, within available funds, a Genetic Blood Disorders program in accord with requirements of Title II of the PHS Act. The program would include both Part A, Sickle Cell Anemia, and Part B, Cooley's Anemia.

Synthesis of Hemoglobin

Research conducted at the National Institutes of Health on Cooley's anemia is carried out in the Molecular Hematology Branch of the National Heart and Lung Institute (NHLI). This program is exclusively involved in clinical and laboratory study of hereditary anemias with primary interest in Cooley's anemia. Any patient with Cooley's anemia, upon referral of his physician and acceptance into the ongoing study, can receive care as part of this program. The Branch also carries out fundamental studies on the underlying defect in Cooley's anemia. NHLI scientists

have synthesized hemoglobin in a cell-free system using components isolated from human red blood cells. These studies have shown that the inherited defect in Cooley's anemia is carried by the genetic molecule messenger RNA and that the cellular defect of the thalassemic cell can be reproduced in a normal cell-free system by the addition of messenger RNA from diseased cells. Studies from several laboratories supported by NIH have now shown that the molecular defect in Cooley's anemia is a deficiency in the amount of normal messenger RNA. Intensive efforts are now being made to develop more effective treatment programs based on this new knowledge.

Outlook

Cooley's anemia is an integral subject of research conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Heart and Lung Institute. The number of Americans afflicted with the disabling and killing disorders of blood, including the anemias, is sufficient to justify the effort. Among the Institutes' research goals is an attack on Cooley's anemia which includes among its goals improved diagnosis, improved methods of detecting carriers of the disease and specific therapy. New research should yield maximal benefits in the number of lives saved today and the deaths prevented in years to come.

CYSTIC FIBROSIS

Although much still remains to be learned about cystic fibrosis (CF), the clinical picture of this inherited metabolic disorder is brighter now than in years past. The exact nature of the basic chemical defect in CF still eludes investigators, but great strides have been made in alleviating the complications of the disease.

Striking one in every 1,500 infants, cystic fibrosis is characterized by malfunctioning exocrine glands that secrete abnormal fluid to internal and external body surfaces, particularly to the gastrointestinal and respiratory mucosal linings and the skin. Research conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), a component of the National Institutes of Health, is aimed specifically at defining the physiologic effects of the clinical manifestations, at determining the biochemical aberrations associated with the disease and at developing improved methods of prompt diagnosis, more effective treatment, and hopefully, eventual prevention of this disease.

In addition to investigations carried out at the National Institutes of Health laboratories and clinics in Bethesda, the NIAMDD supports many cystic fibrosis research projects at medical centers and institutions across the country through the research grant mechanism. This combined effort has opened up promising new avenues which will lead ultimately to the precise definition of the molecular defect in this metabolic disorder.

Obligations for Programs in Cystic Fibrosis

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, and Digestive Diseases...	$2,777,000	$2,525,000	$2,829,000	$2,367,000	2,417,000
Health Services Administration: Maternal and Child Health/Bureau of Community Health Services.	1	1	1	1	1
Total.....	$2,777,000	$2,525,000	$2,829,000	$2,367,000	$2,417,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Cystic fibrosis (CF), an inherited metabolic disorder of exocrine secretion, results in three principal clinical problems. The first is the production of sweat with a high salt content. Because of this defect, patients are unable to conserve salt and are therefore at risk of developing profound dehydration or heat exhaustion in the summer, either of which may be fatal.

The second is that in CF the mucus-secreting glands of the body fail to secrete normal, clear, free-flowing fluid. Instead, they produce abnormally thick, viscous mucus which tends to obstruct the ducts or openings of these glands. When the mucus accumulates in the ducts of the pancreas, it interferes with the ability of this gland to supply digestive enzymes to the intestinal tract, thus leading to poor digestion of food and to malabsorption of a number of essential nutrients. Depending on the severity of this complication, the patient may suffer from general underdevelopment, poor musculature, and retarded bone growth.

The third and most serious complication is the development of progessive, chronic lung disease. Thick mucus obstructs the smaller air passages in the lung, causing labored breathing and chronic cough. In time, bacteria multiply in the accumulated secretions, predisposing the child to chronic bronchitis or pneumonia - a leading cause of death in these patients. The lung changes may also restrict pulmonary blood flow, leading to increased blood pressure in the lung and to consequent chronic heart strain and eventual heart failure.

Current Research Status

Many Institute-supported research projects in CF are related to applications of existing medical knowledge to improved treatment, while other more basic studies involve the search for a specific biochemical defect or genetic abnormality responsible for the disease. Some projects have implications for improving tests for early diagnosis (or developing new ones), for elucidating the specific mechanism of exocrine gland dysfunctions, and for determining the nature of the molecular defect in cell components.

A prime factor in the management of this disease is to establish a correct and early diagnosis prior to the development of irreversible pulmonary complications. The most widely used diagnostic test, based upon an abnormally high concentration of salt in sweat, illustrates one of the manifestations of exocrine gland dysfunction. A number of research projects are concerned with secretory mechanisms, including those of the sweat glands, salivary glands, and those of the respiratory and gastrointestinal systems.

A disease of many disguises, CF offers only enigmatic clues to the disorder's basic mechanism. Promising findings in fundamental research and innovative methods of diagnosis and treatment, however, have opened up new avenues for investigation, resulting in a somewhat more optimistic outlook for patients.

Respiratory Complications

The key to prolonged survival for most cystic fibrosis patients is control of respiratory complications. Chronic pulmonary disease is responsible for death in 90 percent of the cases. Vital respiratory function is the subject of a number of Institute-supported research projects. These include studies concerningpulmonary ventilation, certain complicating, secondary respiratory disorders, cilia of the respir tory mucosa and ciliary movement, and bronchi and bronchial mucus in CF.

Seeking more effective medication for the lower respiratory tract, investigators are evaluating aerosol inhalation therapy. This type of treatment permits small particles of drugs essential for breaking up mucus to penetrate to the lower reaches of the lungs where the air passages are smaller but the surface area is greater.

In addition, research on antibiotics is continuing. A number of safe and effective drugs are in use: resistant strains of micro-organisms, however, which tend to establish themselves in the lungs of patients with CF, particularly pseudomonas and staphylococcus, pose problems in long-term antibiotic therapy. Investigations are underway to evaluate a vaccine against pseudomonas infection as well as the long-term effectiveness of a semi-synthetic penicillin, carbenicillin. Institute investigators have also demonstrated the effectiveness of gentamicin against drug-resistant strains of these two organisms.

Recent research by Institute grantee Dr. LeRoy Matthews and associate Dr. Bernard Boxerbaum has provided one explanation for CF victims' inability to fight off pseudomonas bacteria in the lungs. Studies at University Hospitals of Cleveland have pinpointed a factor in the blood serum of cystic fibrosis patients which appears to inhibit the lungs' defense mechanisms in resisting pseudomonas. The serum, however, has little or no effect on the defensive activity of the lungs against other bacteria.

In CF, the tracheal-bronchial passageways become blocked with mucus, providing a breeding ground for trapped bacteria and other inhaled particles. For unknown reasons, infections in the early stages of cystic fibrosis are almost always caused by staphylococci. As the disease progresses, susceptibility changes primarily to pseudomonas.

The investigators focused on the action of the alveolar macrophages, cells which comprise one of the primary defense mechanisms of the lungs. Rabbit macrophages, when combined with normal blood serum and staphylococcus, and later pseudomonas organisms, killed both forms of bacteria. In CF serum, however, the alveolar macrophages promptly destroyed staphylococci but were significantly less effective against pseudomonas bacteria.

The researchers concluded that childhood treatment of early stage staphylococcal infections with antibiotics may upset the natural defense balance and thereby provide a medium more susceptible to later pseudomonas growth. The studies also revealed that while CF patients may be able to combat successfully pseudomonas bacteria elsewhere in their systems, the lungs are the exception, where macrophages are rendered ineffective. These findings emphasize the importance of continued research on antibiotic therapy, particularly for infections of drug-resistant bacteria.

Pseudomonas Vaccine

Many CF patients (approximately 80 percent) evidence chronic pulmonary colonization with pseudomonas, an organism notoriously resistant to most antibiotics. Recent research by NIAMDD investigator Dr. R. Wood and associates Drs. H. Reynolds and J. Pennington of the National Institute of Allergy and Infectious Diseases measured antibody responses to infection with pseudomonas and to immunization with a vaccine prepared against the species.

Prior to and following administration of vaccine by a series of injections or intranasal spray, antibody levels of CF patients were measured in serum and bronchial secretions. The results indicate that pseudomonas vaccine is well tolerated by both parenteral and intranasal routes, with antibody levels rising significantly following injection. Complete evaluation of nasal administration is underway.

In the group of patients studied, however, no objective improvement in pulmonary function or clinical status was noted, nor was pseudomonas eradicated from any patient's sputum. The investigators concluded that although good antibody responses can be achieved without serious side effects, there is no significant benefit to patients in whom pseudomonas colonization is already well established.

Emphasis is now on the intranasal route of immunization in patients as yet free from pseudomonas. Should the vaccine spray stimulate production of local antibody response in the respiratory tract, an effective immunization program could be established to curb the incidence of new pseudomonas colonizations.

Fiberoptic Bronchoscopy

The development of transnasal fiberoptic bronchoscopy is having a profound effect on pulmonary medicine. The flexible bronchoscope, inserted through the nasal passages down to the bronchial airways, permits bedside and clinic examinations with minimal risk or discomfort.

Dr. Robert E. Wood (NIAMDD) has successfully localized bleeding sites, removed mucus plugs, and obtained secretions for culture and other studies in pediatric patients, with minimal complications. Evaluation of bronchial irrigation to unclog mucus-filled passageways in cystic fibrosis patients is now in progress. The researcher believes transnasal fiberoptic bronchoscopy to be a reliable tool for the diagnosis and management of many pediatric pulmonary disorders.

Mucociliary Transport in Cystic Fibrosis

One such application of the new bronchoscopic technique is observation of the rate of mucus mobility (the normal sweeping motion of the hair-like cilia which line the respiratory airways) and mucus clearance in the bronchial passageways. Chronic obstructive lung disease, one of the most hazardous complications of CF, results from an extremely low rate of mucociliary clearance in these passages.

To measure the rate of airway clearance in adult CF patients, teflon discs were blown onto the tracheal mucosa, and their motion filmed. The findings by NIAMDD investigators Drs. Robert E. Wood, Paul di Sant'Agnese, Philip M. Farrell and associate researchers Judith Hirsch and Adam Warner of the Mt. Sinai Medical Center in Miami indicate that the average rate of tracheal mucus velocity in CF patients is approximately 15 percent of that recorded in healthy persons.

In an effort to improve this rate, patients received a single injection of terbutaline, a bronchodilator which increases expiratory flow rate, with disc movements measured again 15 minutes later. The average mucus velocity doubled in the CF group to one-third that of the normal controls, the first demonstration of pharmacological increases in mucociliary clearance in cystic fibrosis. The investigators believe that further increases may be possible by different drugs, routes of administration, or drug combinations. These observations hold promise in the management of chronic obstructive lung disease, the key to prolonged survival.

Vigorous Therapy Lengthens CF Survivial

Many physicians feel that the prognosis in CF is essentially hopeless, and therefore do not pursue therapy aggressively. To the contrary, a recent epidemiological survey conducted by Dr. Paul di Sant'Agnese and associates of the National Institute of Arthritis, Metabolism and Digestive Diseases indicates that vigorous treatment does increase longevity significantly.

Data were obtained from the National Center for Health Statistics and the National Cystic Fibrosis Foundation on the number of deaths in various age group from 1960 through 1970. Comparison of mortality experience in patients followed in specialized Cystic Fibrosis Centers with patients not treated in such institutions suggests strongly that intensive care results in greatly prolonged survival with an average age at death about ten years beyond that of patients treated outside the Centers.

The study concludes that patients newly diagnosed with cystic fibrosis should be promptly referred to specialized multidisciplinary treatment centers for maximal survival.

Growth and Nutrition in CF Adolescents and Young Adults

Pancreatic deficiency in providing digestive enzymes characterizes approximately 80 percent of cystic fibrosis patients. As a result, much of the daily diet passes through the body undigested, taking with it nutrients needed for adequate growth and development. In very young patients, marked clinical improvement has been noted after initiation of dietary management (reducing fatty food intake) and the addition of pancreatic enzyme supplements. In older patients, however, intolerance to fatty food is less prominent and the state of nutrition is better than that of the younger age group, despite continued loss of fecal fat and nitrogen.

A recent study of fat and nitrogen loss has shown that for the adolescent and young adult cystic fibrosis patient, dietary restrictions and pancreatic supplements have little or no demonstrable effect.

The research by Drs. A. Lapey, J. Kattwinkel, P. di Sant'Agnese and L. Laster, NIAMDD investigators, represents the first comprehensive study of malabsorption in older patients with CF and pancreatic deficiency. The study was designed to evaluate the current clinical status, state of nutrition, and growth achieved in relation to the degree of nutrient loss and adequacy of previous dietary treatment as gauged by the age at diagnosis.

The findings showed that fecal fat and nitrogen loss, frequently massive and widely varied in degree, were present in all study patients regardless of symptoms, state of nutrition, or growth. In fact, many of the patients with better nutrition and prognostic scores had been diagnosed late in life and presumably had not received optimal treatment.

The investigators concluded that these factors did not correlate with the amount of fecal fat and nitrogen loss, adherence to dietary regimen, or adequacy of previous treatment. Rather, the degree of growth failure as well as the state of nutrition was more closely correlated with the degree of severity of pulmonary disease. While pancreatic replacement therapy does improve fecal fat and nitrogen loss somewhat in older CF patients, little dietary restriction is needed, allowing patients to regulate food selection on the basis of symptoms.

Vitamin E Deficiency in Man

The functions of vitamin E in man, at the molecular level, are still unknown, despite the fact that the biological manifestations of vitamin E deficiency are more apparent in various animal species than any other nutrient. Man, however, has not been shown conclusively to develop these symptoms of E deficiency.

Tocopherol (vitamin E) deficiency rarely occurs in normal populations of developed countries. Recent studies, however, by NIAMDD investigators Drs. Philip Farrell, John Bieri, Paul di Sant'Agnese and Dr. Bernard Fisher of St. Louis University have demonstrated that patients with pancreatic insufficiency due to cystic fibrosis are uniformly and profoundly deficient in vitamin E. These patients represent the best available models of human E deficiency which can be studied under controlled conditions.

The studies conducted thus far indicate that vitamin E deficiency in man is associated with many of the findings in animals, such as hemolysis (breakup of red blood cells and separation of hemoglobin from the corpuscles) and evidence of degenerative muscle involvement, but generally at a lower level.

The investigators concluded that patients with CF and secondary tocopherol deficiency should receive vitamin E supplements to correct the condition. The scientists noted, however, that there is little reason to add vitamin E supplements generally in countries such as the United States where people ingest adequate amounts of the vitamin in their diets and have normal blood tocopherol levels, despite the current public fad over vitamin E and "megavitamin therapy."

Blood Polyamines in Cystic Fibrosis

Prevention of CF is unlikely at the present time because of its mode of hereditary transmission. Although effective screening tests have been developed for some other genetic disorders, such as Tay-Sachs disease and sickle cell anemia, a simple and reliable method of detecting carriers of the CF trait so far has eluded investigators.

Recent research by NIAMDD scientists suggests that blood polyamine levels (physiologically active nitrogen metabolites) may be altered in cystic fibrosis patients and in asymptomatic carriers of the disease trait. If such an alteration were consistently demonstrable in the latter group, measurement of polyamines might serve as a CF carrier detection test.

To substantiate this theory, Drs. David W. Lundgren and Philip M. Farrell evaluated polyamine metabolism in cystic fibrosis by measuring the specific blood polyamine, spermine (Sp), and its precursor, spermidine(Spd), in CF patients and carriers. Both groups evidenced increased blood spermidine levels and decreased spermine, leading to significantly altered Spd/Sp ratios as compared to that of normal persons.

The findings thus far suggest that blood levels of polyamines are disturbed in cystic fibrosis patients and carriers. Further study, however, will be required to determine if this apparent abnormality will be useful in population screening for carriers of the CF trait. Moreover, in view of the widespread distribution of polyamines in cells and tissues, further investigations may provide an insight into the nature of the elusive basic defect in cystic fibrosis.

Early Detection

In related research, a clinician at Children's Hospital in Washington, D.C. is testing what may prove to be a reliable diagnostic tool for cystic fibrosis in newborns.

The test, developed in Germany, is based on the principle that in most CF patients the pancreas fails to secrete an enzyme necessary for protein digestion. The experimental detection test indicates the presence or absence of an excessive amount of the protein albumin in the stool, a positive result indicating the need for more extensive examination. The procedure may serve as a valuable adjunct to the standard cystic fibrosis diagnostic test, the sweat test, for excessive salt in perspiration. Although highly accurate in patients three or four weeks of age or older, the sweat test is not suitable for the newborn.

If expanded clinical trials reinforce the initial findings, the new diagnostic tool may enable doctors to initiate immediate therapy and thereby ameliorate or prevent the symptoms of CF. At present, most patients are diagnosed in early childhood, some even as late as the teens, allowing the complications of the disease to take hold. By providing physicians a possible advance warning of the disorder, the "meconium test", if promptly followed with specific treatment, may lead to significantly prolonged survival.

Cystic Fibrosis Bibliography

Through contract funds from the National Institute of Arthritis, Metabolism and Digestive Diseases, the National Cystic Fibrosis Foundation is preparing a comprehensive bibliography on the wide-ranging aspects of cystic fibrosis. The bibliography is designed to make available a consolidated listing of all scientific literature references on the subject, and to serve as an educational stimulus to physicians and investigators in the area of CF and allied health fields. The index should be available for distribution in the fall of 1975.

Outlook

Although much has been accomplished toward alleviating the symptoms of cystic fibrosis, its basic defect and means of permanent control still elude investigators. Malnutrition due to pancreatic insufficiency, formerly a serious complication of the disease, can now be readily managed in most cases by administration of supplementary pancreatic enzymes of animal origin. Through improved antibiotic therapy the consequences of chronic pulmonary disease can now be forestalled in many patients. These measures, and others, have prolonged the life of the cystic fibrosis patient, and have also enhanced the quality of that still unduly short life.

Research is now focused on a wide range of problems. These include refinement of precise screening techniques to identify carriers of the cystic fibrosis trait; identification of the underlying metabolic defect in the disorder; and improvement of antibiotic therapy to retard the progression of chronic pulmonary disease, the most frequent fatal complication of cystic fibrosis. The findings of recent years are contributing to an increasing knowledge base from which the ultimate answer to the cystic fibrosis problem hopefully will come.

DIABETES

Diabetes mellitus is a serious chronic disease which affects over 4-1/2 million Americans. Among diseases, it is the sixth leading cause of death and contributes to heart attacks, stroke, kidney failure, peripheral vascular disease, and blindness. Treatment of diabetes represents only efforts to control the symptoms of the disease. At present there is no known cure. It is essential, therefore, to continue scientific research to find a cure or identify a means of preventing its devastating long-term complications.

Diabetes research at the National Institutes of Health (NIH) is centered in the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). Six other NIH components, notably the National Heart and Lung Institute and the National Eye Institute, also conduct and support research in this field, particularly in the long-range complications of the disease. Recent significant research results include uncovering of additional evidence of a role for glucagon, as well as for the hypothalamic hormone - somatostatin - in diabetes; linking of the onset of diabetes to a prior viral infection; successful transplanting of insulin-producing beta cells in diabetic animals, and further developing an "artificial pancreas."

This ongoing research received encouragement in July, 1974 with enactment of the National Diabetes Mellitus Research and Education Act (Public Law 93-354). The Act calls for development of a long-range plan to expand and coordinate the national research effort against diabetes mellitus; to advance activities of patient, professional, and public education to alert citizens to the early indications of diabetes mellitus; and to emphasize the significance of early detection, proper control, and complications which may evolve from the disease.

Obligations for Programs in Diabetes

	1972	1973	1974	1975 Estimate	1976 Estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, & Digestive Diseases	$8,182,000	$8,235,000	$12,126,000*	$12,222,000*	$13,024,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

A complicated disease, for which there is no known cure, diabetes has been known for some time to be a hereditary disorder. As a result of the body's inability to metabolize carbohydrates normally (which, in turn, is related to impaired production or activity of the hormone insulin), the diabetic patient is unable to convert dietary carbohydrates properly into the stored form, glycogen, or to utilize them normally to produce the energy required for body functions. Thus, the carbohydrates, in the form of glucose, accumulate in the blood and, because of their high concentration,

* Includes $994,000 in 1974 and $14,000 in 1975 from restorations of 1973 impounded funds.

overflow into the urine. As the disease progresses, abnormal carbohydrate metabolism becomes associated with additional derangement in the metabolism of fats and proteins.

"Juvenile Diabetes" is the severe form of the disease which is characterized by onset early in life. This classic type of severe, "brittle" or "unstable" diabetes is usually found in children or young adults with a parent or parents with diabetes or a history of diabetes in their families. If untreated, juvenile diabetes rapidly progresses to a state of grave metabolic imbalance, caused by a relatively severe deficiency in insulin output or severe impairment in insulin activity. One result may be the excessive breakdown of fat with the production of ketone acids which may lead to coma and death unless controlled by insulin administration and other supportive therapy. Patients require lifelong maintenance therapy based on daily insulin injections. This controls the more obvious clinical symptoms and permits the patient to engage in near-normal activities. Nevertheless, patients with juvenile diabetes have a decreased life expectancy and are subject to a gradual onset of progressive changes in various organ systems, the so-called long-term complications. These complications involve a specific abnormality in the small blood vessels of the body characteristic for diabetes, an accelerated degenerative process in the large blood vessels akin to atherosclerosis, and a characteristic, spotty degeneration in the nervous system. With the passage of time, these underlying pathologic processes may progressively result in one or more of the following:

(1) Premature heart attacks, strokes or impairment of the blood supply to the extremities.

(2) Kidney failure.

(3) Progressive deterioration of vision and eventual blindness.

(4) Disabling neuropathies including impotence.

Fortunately the majority of patients with diabetes are afflicted with the more common, less severe type of "Maturity-Onset Diabetes." This form of the disease, as its name implies, usually has a gradual onset in the 50's and 60's and in most cases does not require daily administration of insulin. Many of these patients benefit from reduction in body weight to normal levels. Patients with maturity onset diabetes may also gradually develop some serious long-term complications.

Diabetes is a prime example of a disease in which the research conducted by a number of the Institutes of the National Institutes of Health may be pertinent. Therefore the NIH is establishing mechanisms to ensure coordination of research by the several Institutes concerned.

Diabetes-Endocrinology Centers

In November, 1974 the NIAMDD announced the award of grants to establish four Diabetes-Endocrinology Centers to expand ongoing fundamental and clinical research efforts in diabetes and to expedite the

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flow of scientific information about diabetes from the laboratory to the bedside. The institutions, geographically dispersed, are: the University of Virginia, Charlottesville; Vanderbilt University, Nashville, Tennessee; the University of Chicago, and the University of Washington, Seattle.

These Centers are being established only where a substantial, productive program in diabetes research already exists. An interdisciplinary research effort, the center concept involves many investigators from various departments within the medical schools as well as relevant departments elsewhere in the universities. Such a cooperative effort will bring valuable data from many disciplines into single focus on the problem, will bring about greater efficiency in utilization of facilities and funds, and should stimulate investigators in related areas to contribute to the diabetes effort.

Causation - The Infection Theory

Evidence has been mounting in recent years to suggest that diabetes in genetically prone individuals may be triggered by an infectious process, such as mumps, German measles, or perhaps an influenza-like virus. In some animals, under given circumstances, such viruses seem to disrupt the release of insulin or kill the insulin-producing cells. If such a virus, or viruses, ever is identified in humans, a whole new therapeutic approach to diabetes may evolve.

NIAMDD grantee Dr. Bryce Munger of Pennsylvania State University reported two years ago that healthy guinea pigs become frankly diabetic two to six weeks after being caged with diabetic guinea pigs, or after being injected with urine concentrate from their diabetic counterparts. Efforts to identify an infectious agent or its route of transmission, however, have been unsuccessful.

The infection theory has gained support from the fact that "epidemic" outcroppings of juvenile diabetes are reported periodically in certain areas. In addition, one study conducted in England has found that 85 percent of newly discovered juvenile diabetes cases were preceded by an infection.

Less than six months ago another investigator, now a grant-supported scientist of the Public Health Service, Dr. Harry Sultz of the State University of New York, Buffalo, reported evidence of a link between juvenile diabetes and mumps. If substantiated, this finding might explain why new cases of juvenile diabetes appear in cycles, much like the infectious diseases of childhood.

Dr. Sultz's team of scientists reviewed case histories of 118 children with diabetes in Erie County, New York, and found that half of them had contracted mumps about four years before they showed evidence of diabetes. This finding led to a comparison of the incidence of diabetes with the incidence of mumps over a 20-year-period in Erie County. Here, the investigators also found a correlation. There were corresponding peaks and valleys on the graph of mumps cases which corresponded with the peaks and valleys on the graph of diabetes cases four years later.

From these data the investigators propose that a high incidence of diabetes in boys that occurred in Erie County between 1950 and 1960 was related to the widespread practice at the time of exposing preadolescent

boys to mumps. This practice was followed to reduce the risk of eventual sterility following virus infection of the testes, a possible complication if mumps is contracted after puberty.

Meanwhile, at the University of Vermont, a grantee of the NIAMDD and of the National Institute of Allergy and Infectious Diseases, Dr. John E. Craighead, has shown that genetic factors influence the occurrence of virus-induced diabetes in mice. He has been studying the effects of a diabetes-inducing virus - encephalomyocarditis or EMC virus - in mice of varying genetic constitutions. EMC virus produces a disease in mice which exhibits many features of human juvenile diabetes.

Mice of two different strains, when inoculated with the virus, developed systemic infections, and, in the course of the infections, virus multiplied to a similar extent in animals of both types. Mortality, however, was greater and blood glucose levels were abnormally high in one strain, while blood sugar levels remained normal in the other strain. Data obtained in further study suggest that production of diabetes by EMC virus is influenced not by a single genetic factor, but rather by several genes acting in concert.

Not all attempts to demonstrate such correlations have been successful, however. The NIAMDD Epidemiology and Field Studies Branch in Phoenix, Arizona, conducted a study on the prevalence of diabetes in the residents of the Pribilof Islands, a relatively isolated population, 5 years subsequent to an epidemic of coxsackie B4 infection, but could find no relationship between new cases of diabetes and the earlier coxsackie B4 infection. This population suffered an epidemic of mumps at approximately the same time and evaluations will also be made to examine the possible effect of mumps on the development of diabetes.

In addition, Dr. Craighead at the University of Vermont is beginning a retrospective 10-year survey and analysis of clinical records on juvenile diabetes in regard to virus infection preceding onset of diabetes in children.

Another grantee, Dr. Sidney Kibrick, Boston University, has also begun a comprehensive study to explore the relation between diabetes mellitus and coxsackie B viral infection in mice genetically predisposed to diabetes.

The results to be forthcoming in the next 2 to 3 years from these Institute-supported studies should be extremely informative in clarifying whether or not the premise of a viral origin for a proportion of the incidence of diabetes mellitus is viable.

Diabetes - A Bihormonal Disorder?

In 1971 Dr. Roger Unger, a NIAMDD grantee at the University of Texas, Dallas, reported that diabetes is characterized by excessive glucagon secretion, in addition to insulin deficiency, and thus may be a bihormonal disorder. (Glucagon, a hormone secreted by pancreatic alpha cells, stimulates release of glucose from the liver and tends to elevate blood glucose levels).

In subsequent studies Dr. Unger linked glucagon excess to infection, which often results in deterioration of blood sugar control in diabetic patients, and to diabetic ketoacidosis (increased ketoacid production) which requires emergency therapy.

Another recent study by an Institute grantee, Dr. Peter Forsham of the University of California, San Francisco, demonstrated that infusion of the hypothalamic hormone, somatostatin, into normal human subjects results in a lowering of both plasma glucagon and glucose levels. He subsequently showed that infusion of somatostatin into diabetic patients decreased plasma glucagon levels by 50 percent and plasma glucose levels by 25 percent. Moreover, somatostatin combined with insulin was more effective than insulin alone in diminishing the elevated blood glucose levels associated with meal ingestion. These research studies suggest that somatostatin, possibly in some longer-acting form, may prove to be a useful adjunct to insulin.

Meanwhile, at the University of Washington, NIAMDD grantees Dr. John Ensinck and Dr. Charles Goodner have observed that among known inhibitors of insulin or glucagon secretion, somatostatin appears to be unique in that it inhibits both hormones, whereas others inhibit selectively. The scientists, who are studying the effects of somatostatin in baboons, have issued a precautionary warning to investigators using somatostatin in human patients, however. Their preliminary studies have revealed that only a three-hour infusion of the hormone in baboons may significantly reduce blood platelets and increase the likelihood of bleeding.

With the recent discovery of somatostatin new aspects of the mechanism of the natural history of diabetes are being revealed. Recent work from Dr. Unger's laboratory has demonstrated that maintenance of normal blood glucose levels depends on the coordinated actions of both glucagon and insulin, and puts a different emphasis on the mechanism of the increased blood glucose in fasting diabetics. The reason for this fasting high blood sugar could therefore be inappropriately high glucagon levels.

Thus, glucagon and insulin provide, via their antagonistic actions upon glucose balance in the liver, a means by which glucose turnover can be changed without a major perturbation of glucose concentration.

For example, when both insulin and glucagon increase symmetrically, as happens during the ingestion of protein, both glucose production and glucose utilization increase symmetrically, but blood glucose concentration remains unchanged. Conversely, when both insulin and glucagon are decreased symmetrically (as in the case of somatostatin infusion to inhibit secretion of both hormones) the effect is a fall in both glucose production and glucose utilization, with but minor change in blood sugar levels.

Work from Dr. Unger's group has shown in experimental animals that when both insulin and glucagon are inhibited by infusion of somatostatin, normal glucose levels are maintained. Only if suppressed levels of glucagon are raised to normal by infusing glucagon does hyperglycemia (elevated blood sugar) appear. These new developments suggest that glucagon may have a far more important role in the genesis of diabetic hyperglycemia than had previously been suspected.

6

Transplantation of Insulin-Producing Cells

Logically, the implantation of a normal healthy pancreas in a juvenile diabetic patient should modify and ameliorate his diabetes. Although this procedure has been attempted in a number of patients with severe diabetes, the grafted organs, in every instance, eventually were inactivated by the transplant rejection reaction of the patient's immune mechanisms.

Therefore, several groups of research scientists are attempting to find a satisfactory method of transplanting only the insulin-producing, beta cells of the pancreas. It is hoped that such a procedure will result in improvement of diabetic control, as well as in prevention of the secondary complications of diabetes, such as kidney failure or vascular damage.

Two years ago, Drs. Walter Ballinger and Paul Lacy, NIAMDD grantees at Washington University, St. Louis, reported preliminary success in transplanting such cells from normal rats to diabetic rats of the same genetic strain. Transplantation into pockets in the thigh muscles or into the peritoneal cavity resulted in a temporary, significant reduction of blood and urine glucose levels, and restoration of weight gain, but the host animals still exhibited abnormal glucose tolerance.

The Missouri scientists more recently have described direct "implantation" of beta cells into the liver of diabetic rats by their injection into the portal vein. This approach has led to a marked fall in blood glucose levels and abnormal urine output, restoration of weight gain, and nearly normal results in glucose tolerance tests. Such improvement lasted for at least three months and several animals survived as long as nine months.

One recurring obstacle in such research has been the beta cell harvesting techniques, which have produced very low yields and necessitated the use of multiple donor animals for each transplantation procedure. Now the same investigators have developed a new digestion-filtration technique for isolating beta cell islets which yields sufficient islets for single-donor transplantation. Transplantation of these islets from normal Rhesus monkeys to diabetic Rhesus monkeys has resulted in significant reversal of the diabetic state in all animals. Recipient monkeys immediately became more active in their cages, and excessive thirst and urination, and elevated blood sugar levels (all symptoms of diabetes), were reduced. Intravenous glucose tolerance tests performed one week after transplantation showed significant improvement. This animal model now can be used for additional long-term studies before islet transplantation in human diabetic subjects is considered.

Another Institute grantee at the University of Minnesota, Dr. Arnold Lazarow, reported last year that diabetes had been ameliorated in adult rats following transplantation of islets of beta cells derived from immature pancreases of newly-born rats into the peritoneal cavity.

This past year, a grantee of the National Institute of Child Health and Human Development, Dr. William Clark of the University of California, Los Angeles, successfully treated diabetes in adult rats by transplanting whole pancreases taken from genetically compatible rat fetuses of gestational ages 17 to 18 days. Either complete or partial control of the

disease lasted up to 165 days in 64-percent of transplant recipients, and the tissue transplants continued to function successfully nine months after transplantation.

These successful results with fetal tissue may be due in part to a special property of the fetal tissue; however, in both instances highly inbred rats were used and one would thus expect fewer problems with immune rejection mechanisms.

A Note of Warning

As exciting as beta cell transplantation and whole organ transplantation appear to be on the surface, the NIAMDD in conjunction with the American Diabetes Association has been compelled to sound a warning about optimistic speculation in conjunction with such findings. They have cautioned that success in total or sub-total transplantation of the pancreas in humans has been "exceedingly limited" and not to be considered a form of treatment for human diabetes.

Such transplantation, including islet cell transplantation, is a highly experimental procedure and further extensive animal experimentation must be conducted to assure safety. Such research in human beings is regarded as premature because of serious problems of tissue incompatibility. Any experimentation concerning humans, it is noted, should be carried out only by research teams after review by a board on human research.

"Artificial Pancreas"

Two years ago a long-time NIH grantee at the University of Southern California, Dr. Samuel Bessman, devised a blood sugar sensor capable of continuously monitoring glucose levels in the blood and other body fluids. This accomplishment was viewed as the first practical step toward eventual development of an "artificial pancreas," an implantable device which would be controlled by an automatic blood glucose level sensing mechanism and would be capable of delivering insulin automatically to the insulin-dependent diabetic patient at the moment he needs it and in the exact dosage required.

Recent research by a number of other investigators has brought additional developments in efforts to devise a computerized, insulin-stocked "artificial pancreas." Dr. Stuart Soeldner of the Joslin Diabetes Foundation, Boston, for example, has implanted a glucose sensor in monkeys and has kept one there for as long as four months before rejection occurred. In rats and rabbits, futhermore, he has wired the sensor to an implanted, tiny radio transmitter with which to transmit outside the body continuing information on blood sugar levels.

Meanwhile, Miles Laboratories, in collaboration with the University of Toronto, has produced a laboratory "artificial pancreas" for use in hospitalized diabetic patients. This device monitors blood sugar levels and dispenses insulin or glucose as required. Thus far, it has been used successfully on nine hospitalized diabetic patients in West Germany.

In Toronto, a second prototype of the same device has undergone successful clinical trials in a dozen juvenile diabetics. University of Toronto scientists, led by Dr. A. Michael Albisser, designed and developed the artificial organ's complex hardware, while Miles Laboratories

incorporated the entire device into a single unit. It must be emphasized, however, that these experimental devices are interesting and useful laboratory machines of large size to which the patient must be connected, and he must remain in a restrictive hospital setting as long as he receives his experimental and temporary treatment.

Most of the investigators involved in such research now estimate that it will require many years before a fully miniaturized, implantable artificial pancreas, which will work effectively and for more than just brief periods of time, will be ready for human clinical trials.

Juvenile Diabetes in Remission

Juvenile diabetic patients who are dependent upon insulin and who are prone to develop ketoacidosis are generally characterized by rapid onset of their illness and by nearly complete failure of the insulin-producing pancreatic beta cells. Temporary remission of diabetes occurs in one of five such patients, however, shortly after disease onset.

In recent studies of this poorly defined remission state NIAMDD grantee Dr. Stuart Soeldner of the Joslin Diabetes Foundation has found that most patients in remission show substantial insulin release responses to glucose and to meal ingestion, and near-normal responses to administration of insulin. His findings support the concept that clinical remission in such cases of recently emerged juvenile diabetes is dependent on a functional recovery of the insulin-producing beta cells, and indicate that the significant "insulin resistance" of severe diabetes is not present in this early remission state.

Knowledge that a functional recovery of the beta cell and unimpaired insulin sensitivity play important roles in the maintenance of the clinical remission state may lead to several new research approaches to the problems presented by diabetes.

Complications of Diabetes

As noted earlier in this report, despite apparent control of the obvious clinical symptoms of diabetes, progressive changes apparently occur inexorably, especially in juvenile diabetes, that may lead to gradual deterioration of blood vessels, kidneys, the nervous system and the eyes. Thus, a great many investigations are devoted to learning more about these serious complications and, hopefully, to preventing them.

For example, NIAMDD grantee Dr. Donald McMillan of the Sansum Medical Research Foundation, Santa Barbara, California, has recently reported that serum viscosity is significantly increased in diabetic patients compared to both healthy subjects and patients with diseases other than diabetes. Moreover, this increased serum viscosity is even greater in diabetic patients with clinically detectable small blood vessel disease. Dr. McMillan suggests that the observed increase in serum viscosity might be a part of the metabolic disturbance of diabetes, and that it could play a role in the development of diabetic microangiopathy, or small blood vessel disease.

Studies being conducted at New York Medical College, meanwhile, point towards new ways of decreasing the incidence of damaged blood vessels in diabetics. In a strain of mice with genetic diabetes, Dr. Rafael Camerini-Davalos, an Institute grantee, has reduced the occurrence of kidney complications by half, from 80 percent to 40 percent, by treating the mice with pyridinolcarbamate. By contrast, the occurrence of kidney complications among untreated diabetic mice ranged from 67 to 85 percent.

Treatment with the new drug apparently normalized the activity of a specific enzyme - glucosyltransferase - in the liver, the activity of which had been significantly increased prior to such therapy. This increased enzymatic activity appears to be one of the first abnormal steps in the blood vessel damage caused by diabetes. If such increased activity of this enzyme is inherited in human subjects as it is in the mice studied by Dr. Camerini-Davalos, then he and his associates have observed for the first time a mechanism for the possible prevention of blood vessel damage resulting from diabetes.

Outlook

Diabetes gained renewed national attention in 1974 with passage of the National Diabetes Mellitus Research and Education Act. This legislation calls for a broadening of diabetes-related activities, including the preparation of a National Diabetes Plan, in the near future. A yearly report to the Congress will continue to give an accounting of NIH's research activities. At the rate at which diabetes research is and has been proceeding in recent years, it can be hoped that deferment of its onset in predisposed persons and suppression of its severe complications are within the realm of possibility.

DIGESTIVE DISEASES

Digestive diseases encompass disorders of the esophagus, stomach, intestine, colon, liver, gallbladder and pancreas. Included in these disorders are familiar diseases, such as peptic ulcer, hepatitis, cirrhosis of the liver, gallstones, Crohn's disease and ulcerative colitis. The causes are many and various: infections, cancer, alcoholism, genetic defects and reactions to life stress.

Although diseases of the gastrointestinal tract are among the most common illnesses in the country, second only to diseases of the heart and circulation in the number of physician office visits or house calls they require, many of these ailments are poorly understood. Diseases of the stomach and intestines may afflict persons of any age, but most often affect those in the middle-aged group at the peak of their most vigorous and productive periods, often causing prolonged and expensive hospitalization and out-patient treatment and countless social and emotional problems. Some diseases such as ulcerative colitis are of a chronic nature. Many patients are afflicted for years and may have to undergo extensive and repeated treatments and surgery.

Obligations for Programs in Digestive Diseases

	1972	1973	1974	1975 Estimate	1976 Estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases..	$16,404,000	$16,240,000	$22,467,000*	$18,288,000	$18,836,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Arthritis, Metabolism, and Digestive Diseases

Although digestive diseases tend to be chronic instead of fatal, they affect 13 million Americans and are of enormous economic cost in direct medical costs and in time lost from work. This cost is estimated at $16.5 billion in 1973 or about $80 for every American. Over 10 percent of the cost of American medical care is for digestive diseases. One-ninth of hospital admissions and almost one-third of all surgery are for digestive diseases. One-quarter of cancer deaths are due to malignancies in the digestive system. Add to this toll cirrhosis of the liver, which is the fifth most common cause of death in men in the United States, and peptic ulcer, which strikes one of every ten men at some time during their lifetime, and the impact of digestive diseases on the health of the nation is impressive.

The annual economic loss due to peptic ulcer and its complications of hemorrhage and perforation, with resultant need for surgery, is estimated at just under $1 billion. The loss due to digestive disease-related disability and loss of income due to premature death has been calculated at $16 billion annually. Of all disease categories, digestive disease ranks third in causing economic loss, exceeded only by cardiovascular disease and accidents.

* Includes $2,579,000 in 1974 from restoration of 1973 impounded funds.

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) bears primary responsibility for the Federal Government's research in the field of digestive diseases.

The Institute's program of extramural grants to scientists at research centers across the country supports investigations of a broad array of ailments of the digestive tract. Research progress is being achieved through intensive and comprehensive laboratory experiments and clinical trials. This past year, these investigators have contributed numerous important findings.

Dissolving Gallstones

Digestive diseases are as complex from the standpoint of the biomedical research investigator as they are from the point of view of the practicing physician. For example, little is known about how gallstones are formed, but gallstone disease ranks fifth among causes of hospitalization. About 15 million Americans have gallstones; in many cases they cause no symptoms while in others they result in debilitating disease. Surgery is the standard form of treatment and some 375,000 gallbladder operations are performed each year at an average cost of $2000 each. Inasmuch as many gallstone patients are poor surgical risks and an estimated 6,000 patients die each year after surgery, an alternate way of controlling the disease has long been sought.

NIAMDD grantees Drs. Johnson L. Thistle and Alan F. Hofman and associates at the Mayo Clinic, Rochester, Minnesota, reported two years ago that long-term oral administration of a primary bile acid, chenodeoxycholic acid, can result in dissolution of long-standing cholesterol gallstones. Their present study was designed to determine if patients treated successfully with this agent might relapse when such therapy is discontinued. After chenodeoxycholic acid administration was stopped, bile from such patients reverted to its pre-treatment state of being supersaturated with cholesterol, altered bile acid composition induced by therapy was reversed, and new gallstones developed in several patients. These observations illustrate the need for controlled long-term studies to assess the efficacy and safety of chenodeoxycholic acid therapy, and the possible need for a prophylactic maintenance regimen after existing cholesterol gallstones have been dissolved successfully.

In another development, the Institute has awarded a contract to Cedars-Sinai Medical Center in Los Angeles to supervise and participate in a long-term collaborative clinical study of the feasibility, effectiveness and safety of dissolving gallstones with the aid of chenodeoxycholic acid. It is anticipated that the contract-supported study involving several participating medical centers will run for approximately five years and will ultimately be a multi-million dollar project.

Peptic Ulcer Study

One of the Institute's main goals is to lessen the toll that peptic ulcers now exact in deaths, sickness and dollars. About 10 million Americans are estimated to have ulcer symptoms on an intermittent basis and each year about 10,000 Americans die of complications of peptic ulcer.

A major attack on this 20th century plague was launched last April with the establishment of a Peptic Ulcer Center to be operated jointly

by the UCLA School of Medicine and the Veterans Administration Wadsworth Hospital Center in Los Angeles, with Dr. Morton I. Grossman as Program Director. The five-year study supported by a sizeable Institute grant involves 10 key investigators with multidisciplinary expertise, and may ultimately gain support totalling more than $4 million.

With an integrated program that will foster cross-disciplinary investigation, peptic ulcer will be studied from various approaches. Examples of fields of study include: movement of hydrogen ions across normal and diseased mucus membranes; pathogenesis and treatment of lesions of the stomach and duodenum; psychosomatic factors in causation and recurrence of peptic ulcer; and study of defined populations over long periods to determine prevalence and incidence of peptic ulcer.

Through these interdisciplinary studies at increasing levels of organization from cells, tissues, animals, man and finally entire populations, researchers expect to gain new insights into the causes and natural history of peptic ulcer, and to apply this knowledge to improvements in its diagnosis, medical and surgical treatment, and prevention.

Promising Peptic Ulcer Treatment

Last year it was reported that British scientists had developed a new, different, antihistaminic drug, metiamide, which, in animal studies, proved capable of completely blocking histamin-induced gastric acid secretion. More recently, NIAMDD grantees Drs. John S. Fordtran and C. T. Richardson of the University of Texas, Dallas, have shown in preliminary clinical trials that metiamide effectively blocks such secretion in man.

Studies of the effect of metiamide on food-stimulated acid secretion in duodenal ulcer patients have now revealed that this agent suppresses such secretion below the level believed necessary to develop or to maintain a duodenal ulcer. Since a transient adverse affect has been observed, however, in a few patients in England on long-term therapy, use of this agent has been temporarily suspended in the United States. Agents with a similar action but which are devoid of this potential toxicity are now being sought.

Gastrin and Peptic Ulcer

A whole family of gastrins, the gastrointestinal hormone which stimulates acid secretion by the stomach, is evolving as more sophisticated techniques develop in peptide separation and in radioimmunoassay studies. The present array of biologically active peptides ranges from "minigastrin", to "gastrin", to "big gastrin", to "big-big gastrin" depending on the size of the particular molecule. The principal question now is understanding the biological significance, potency, duration of action and metabolism of each of these related compounds. NIAMDD grantees Dr. Morton I. Grossman and his associates at the Peptic Ulcer Center, UCLA, have made an auspicious start in this direction.

The researchers have now found that, when circulating concentrations of gastrin are measured, that "gastrin" has about five times the potency of "big gastrin" in its acid-stimulating action.

Recognition of differences in biological potencies of the various circulating forms of gastrin, and the ability to separate these forms, may help unravel the mystery of why some people with normal total serum gastrin levels still show excessive secretion. For example, future research may show that some persons have a predominance of "gastrin" rather than "big" gastrin in their circulating blood.

New Active Peptide

A new biologically active peptide, "vasoactive intestinal peptide" (VIP) originally isolated from the small intestine of hogs, is now vying for a place as a bona fide hormone. The synthesis of this peptide has already been accomplished by NIAMDD grantee Dr. Miklos Bodanszky, Case Western Reserve University, Cleveland. It is structurally related to that family of gastrointestinal hormones that includes secretin, glucagon and gastric inhibitory peptide and shares many of their actions. It has been shown to cause a striking water and electrolyte secretion in the small intestine of dogs.

Elevated plasma levels or a high pancreatic tumor content of VIP have been reported in six patients with watery diarrhea associated with the so-called pancreatic cholera syndrome. An NIAMDD grantee, Dr. Daniel Kimberg formerly of Beth Israel Hospital (Harvard Medical School), Boston, is investigating the mechanism whereby this natural substance acts on gut secretion to cause watery diarrhea. Based on results obtained thus far, this new peptide is thought to be related to the diarrhea in the pancreatic cholera syndrome.

Controlling Gastrointestinal Bleeding

Conservative methods of treating acute, upper gastrointestinal bleeding remain unsatisfactory and surgery is often the only alternative. Corrective surgery is often poorly tolerated by an already critical ill patient, however, and a new method of stopping acute gastrointestinal bleeding is needed.

Angiographic techniques together with intra-arterial infusions of vasconstricting drugs was introduced by a NIAMDD grantee in 1968 as a means of arresting bleeding from the gastrointestinal tract. Now NIAMDD grantee Dr. Stanley Baum of Massachusetts General Hospital, Boston, has successfully used this procedure to control acute, unremitting GI bleeding in 31 of 37 patients. The technique (using posterior pituitary extract) provides an alternative to surgery in selected patients.

Gout Remedy Relieves Familial Mediterranean Fever

The antigout drug, colchicine, has been used successfully to treat familial Mediterranean fever (FMF) in the first controlled trial of any therapy for this disease, a National Institutes of Health investigator reported. FMF is an inherited disease found among persons of Mediterranean parentage; it is characterized by attacks of severe pain in the abdomen or chest with prostration and fever. Attacks subside after a few days and recurr at unpredictable intervals.

Although many agents have been considered of value in treating FMF since the discovery of this disease in 1908, it has remained a disorder of unknown origin that until recently defied the best diagnostic and therapeutic approaches.

Dr. Sheldon M. Wolff and associates of the National Institute of Allergy and Infectious Diseases have now reported the results of a controlled, double blind trial, in which colchicine was used to reduce the number of attacks of FMF in patients known to have the disease.

Courses of colchicine or placebo (inert substance) were assigned randomly to 11 patients with long-standing FMF. Patient data revealed striking results: during 60 courses of "treatment" with placebo, 38 were terminated by attacks, while during the same number of colchicine courses, only 7 attacks occured.

Virus Causes Infant Diarrhea

Severe diarrhea in infants and young children can be life-threatening but, in the majority of cases, no causative agent can be found. Recently, Australian, English, and Canadian scientists have reported the presence of a small reo- or orbivirus-like particle in fecal extracts obtained from very young patients with acute gastroenteritis. The Australian group also found the particles in intestinal cells and the Canadians in intestinal fluids.

National Institute of Allergy and Infectious Diseases and D.C. Children's Hospital scientists have now obtained convincing evidence that the reovirus-like particle observed in the stools of young children hospitalized with severe diarrhea is the actual cause of the disease. In the course of these studies, the investigators also developed a laboratory test which should enable epidemiologists to determine to what extent the particle causes infant diarrhea across the country and around the world.

In the present study of infant gastroenteritis, NIAID scientist Dr. Albert Z. Kapikian, employed a technique known as immune electron microscopy (IEM) and, for most stool filtrates, conventional electron microscopy as well. Dr. Kapikian and associates have been successful, previously, in using IEM to uncover the agent causing an outbreak of gastroenteritis in Ohio, and also used the technique to visualize the virus causing infectious hepatitis.

Immune electron microscopy involves the use of convalescent serum, which usually contains antibody specific for a causative organism. This antibody, in a mixture with infective material, coats the infecting particles and enables the visualization, not usually possible by conventional electron microscopic examination, of a very small virus even when present in small numbers.

Digestion of Dietary Fat

It is generally believed that dietary triglycerides (the common edible fats and oils), once ingested, are not appreciably affected by digestive enzymes until they reach the duodenum. Almost two years ago, however, NIAMDD scientists reported that the serous glands of the rat

tongue secrete a potent enzyme that converts (digests) dietary trigylceride to partial glycerides (mostly diglycerides) and free fatty acids in the stomach.

NIAMDD scientists Drs. Robert O. Scow, Margit Hamosh and Hayden L. Klaevaman now report that esophageal aspirates obtained from human subjects contain a lipolytic activity similar to that found in the tongue and pharynx of the rat. Glands in or near the pharynx secrete a pharyngeal lipase which acts in the stomach (and upper duodenum) to hydrolyze dietary triglyceride to partial glycerides and free fatty acids; this reaction is first step in the digestion of dietary fat in man.

Inflammatory Bowel Disease

Both ankylosing spondylitis and a peripheral joint arthritis occur in many patients with chronic inflammatory bowel disease. In an earlier study NIAMDD grantee Dr. Paul I. Terasaki of the University of California, Los Angeles had described a remarkable association of a so-called HLA histocompatibility antigen, W27, found in the blood and tissues of certain individuals with ankylosing spondylitis (arthritis of the spine which leads to immobilization of spinal joints). This led directly to research to determine their exact relationship.

He now reports that most patients (75 percent) with inflammatory bowel disease and spondylitis are W27-positive, while those patients with inflammatory bowel disease and peripheral arthritis are W27-negative. Thus, the W27 antigen may be a useful clinical and pathogenetic indicator that distinguishes between the joint diseases that occur concurrently with inflammatory bowel disease. Moreover, it also identifies a subgroup of patients highly susceptible by inheritance to development of spondylitis but not peripheral arthritis. The broader significance of this work is that now arthritis investigators are looking for other genetic biochemical markers which will indicate the susceptibility of individuals to various types of arthritis, with the hope in mind of finding ways either to protect such individuals against arthritis or to lessen the severity of disease when it occurs in them.

Antibiotics Needed in Colon Surgery

The controversy over the value of antibiotics in large-bowel surgery is finally nearing a settlement. Three surgical groups, two in the U.S. and one in Britain, have now reported that properly tailored antibiotic treatment of patients who undergo colon surgery can reduce the risk of infection and can prevent complications.

For some time, previous studies have hinted at this conclusion; but until the appearance of the three more recent reports the issue remained clouded by the lack of fully controlled, randomized studies. The groups from the University of Leeds in England and the Mayo Clinic not only filled this gap but arrived at the same conclusion: that antibiotics do play an essential role in controlling the microbial flora of the large bowel, but to be fully effective, both teams believe that drug preparation must be combined with carthartics and enemas. Further confirmation of

this view came from a third report by NIH grantee Dr. I. Cohn Jr. of Louisiana State University, Baton Rouge. Over the years the LSU group has used some 50 different antibiotics alone and in combination during the course of its studies. They concluded that antibiotics do play a vital role in controlling large-bowel flora, and indicated that kanamycin was the most effective antibiotic in eliminating large bowel bacterial flora prior to surgery.

LIVER DISEASE

The liver performs a multitude of complex biochemical tasks without which life cannot exist. The largest single organ in the human body, the liver functions as a "chemical factory," as a clearing station for purification and detoxification of blood, as a storage house for certain nutrients (particularly carbohydrates, certain minerals, and vitamins), as a site of production of blood proteins, as a secretory gland which aids both digestion and the removal of wastes, as well as for a myriad of other metabolic functions. Not surprisingly, an organ of such complexity is subject to a great many injuries and diseases.

Liver Transplants

In 1968, NIAMDD supported scientist Dr. T.A. Starzl and associates at the University of Colorado Medical Center, Denver, reported the first successful liver transplantations in four children in whom the transplanted organs remained functional for periods up to one year.

As of March, 1974, some 39 transplant teams have done 201 liver transplants in 195 patients. Fifteen patients are still alive with functioning grafts, the longest survivor harboring a five year old graft.

Although as yet liver transplantation has not proved to be practical therapy because of the many difficulties associated with the procedure research in this important area continues.

Alcohol and Liver Disease

In 1973, Institute grantees Drs. Charles S. Lieber and Emanuel Rubin of Mt. Sinai School of Medicine, New York, N.Y., produced for the first time alcoholic hepatitis in baboons by giving them alcohol in combination with a nutritionally adequate diet. In man, alcoholic hepatitis and fatty liver precede alcoholic cirrhosis and it was significant that the experimental animals also eventually developed cirrhosis. The researchers have also produced evidence suggesting that alcohol consumed by chronic drinkers might have an injurious effect upon cells of the small intestine strikingly similar to the damage to liver cells that which often occurs in alcoholics. They were able to demonstrate the damage even in non-drinkers after exposure to relatively limited periods of alcohol intake.

The same team now has produced the entire spectrum of alcoholic liver injury over a four-year period in baboons, including fatty liver in all 13 test animals, alcoholic hepatitis in four, and cirrhosis in

two. The data suggest that contrary to a long-held belief, a nutritious diet will not prevent development of alcoholic hepatitis and cirrhosis when excessive amounts of alcohol are chronically consumed.

Treatment of Alcoholic Cirrhosis

The two principal liver diseases, cirrhosis (on the increase in our adult population) and hepatitis (increasing at an alarming rate among our young population) are both crippling and occasionally fatal afflictions of great social and economic importance.

A diet containing medium-chain triglycerides (MCT) (a man-made mixture of fats characterized by smaller-sized fatty acid molecules) has produced significant changes in the fatty acid composition of liver lipids in alcoholic patients with cirrhosis. Such a diet also has increased previously depressed serum albumin levels, a change which is believed to correlate with recovery of liver function.

Institute grantee Dr. Frank L. Iber, formerly of Tufts University Medical School, Boston Mass., and associates reported the above findings which suggest that the MCT diet may have potential value in the treatment of alcoholic cirrhosis, which claims the lives of some 32,000 Americans each year.

Wilson's Disease

Wilson's disease is an inherited, progressive neurologic and liver disease caused by faulty copper metabolism and abnormal copper accumulation in body tissues and in vital organs such as the liver, kidneys, brain and eyes. Heretofore it has been assumed that the underlying biochemical problem is a deficiency in the formation of a specific serum protein, ceruloplasmin, which normally binds the small amount of copper in circulation and plays a critical role in the quantitative regulation of the absorption of dietary copper.

NIAMDD grantee Dr. K. Michael Hambidge of the University of Colorado Medical Center, Denver, has shown that metallothionein, a metal-binding protein isolated from the livers of Wilson's disease patients, has a four-fold affinity for copper compared with its counterpart from normal control subjects. This finding suggests that in Wilson's disease, an abnormal metallothionein with a highly increased affinity for copper may be a causative factor.

An abnormal protein with increased affinity for copper could explain many of the defects in copper balance. In the normal liver copper is either stored, incorporated into enzymes, or excreted. The abnormal protein, however, probably causes the liver to retain copper and to decrease its normal incorporation into serum ceruloplasmin. Retention of an abnormally high copper load in the liver eventually leads to destruction of liver cells and impairment of normal liver function. Whether such a protein also is involved in accumulation of copper in the brain, kidneys and cornea is as yet unknown.

Hepatitis Transmission by Dentists

Although serum hepatitis is usually spread by the parenteral route, through introduction of the causative virus into blood on tissues of a

susceptible individual by way of puncture of the skin, its transmission by nonparenteral routes is well established. Recent investigations have established that "hepatitis B" (serum hepatitis) can be conveyed to others during coitus via the man's semen and through saliva and respiratory droplets. Recently another mode of transmission has been found. NIAMDD supported scientists Dr. Michael L. Levin and associates of Johns Hopkins University, Baltimore, Md., reported an outbreak of HB Ag hepatitis that began in a dental office and was transmitted to 13 dental patients. After ruling out dental instruments as potential carriers, it was concluded that the most likely mode of transmission was via small cuts and abrasions on the hands of the dentist, an oral surgeon subject to such lesions.

Bile Acids In Liver Disease

Chronic active liver disease is characterized by clinical and biochemical features of continuing liver inflammation. Remission is often achieved with steroid drug therapy. During such treatment conventional liver-function tests usually indicate normal values before histologic remission occurs. Hence, these tests are not true indicators of cellular disease activity.

Recent studies have demonstrated that measurement of serum bile acids may be useful in the diagnosis of liver disease. Research by Dr. Alan F. Hofmann and associates of the Mayo Foundation, Rochester, Minn., indicates that elevated serum levels of conjugates of cholic acid appear to provide a more sensitive indication of active hepatitis than conventional liver function tests.

Removing Substances from Blood During Liver Failure

Metabolic waste products and toxins are eliminated from the body predominantly by the kidney and the liver. While hemodialysis is an effective method of removing low molecular weight substances from the blood when kidney function is inadequate, there is no similar procedure for removing protein-bound substances such as bilirubin when liver function is impaired.

Research by NIAMDD scientists Drs. Paul H. Plotz and Paul Berk and associates have introduced the use of affinity chromatography as a new approach to the removal of protein-bound metabolites and toxins from the blood of patients with liver failure. Their work involves the efficient removal of bilirubin and other protein-bound substances from plasma and blood in vitro laboratory tests, by filtration over agarose beads (an insoluble sugar-like substance) which have been coated with the blood protein albumin, and in experimental animals by perfusion of extra corporeal ("extenionized") blood over columns of such beads before it is re-infused. Such a procedure may prove useful for removing protein-bound substances from the blood of patients with liver failure, in cases of intoxication with protein-bound drugs, or specific metabolic deficits.

Outlook

The National Institute of Arthritis, Metabolism, and Digestive Diseases is committed to a coordinated program aimed at conquering a host of devastating chronic digestive diseases. New ideas, techniques and research findings developed by grant-supported and intramural scientists will help result in a more complete understanding and improved treatment for these disorders.

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KIDNEY DISEASE AND ARTIFICIAL KIDNEYS

Chronic, or end-stage, kidney failure is the common final event of many different kidney diseases. While methods are being developed to save and extend the lives of many people with end-stage kidney disease, some 60,000 Americans die annually from irreversible kidney failure. The kidneys play a central role in maintaining body functions and the body's internal chemical equilibrium. They remove end products of metabolism from the blood and maintain a number of other essential physiologic processes. Kidney diseases, as well as other systemic and metabolic diseases may drastically alter vital kidney functions. When the disease is chronic and progressive, symptoms ultimately evolve in a final pattern of end-stage disease with irreversible kidney failure and its characteristic symptom complex, uremia. The National Institute of Arthritis, Metabolism, and Digestive Diseases is the focal institute at the NIH for kidney research and diseases of the urinary tract. It shares responsibility for certain specialized aspects of kidney research with the National Heart and Lung Institute and the National Institute of Allergy and Infectious Diseases.

Obligations for Programs in Kidney Disease and Artificial Kidneys

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, & Digestive Diseases	$18,127,000	17,726,000	21,404,000*	16,729,000	17,592,000

* Includes $2,552,000 in 1974 from restoration of 1973 impounded funds.

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES

KIDNEY DISEASE AND ARTIFICIAL KIDNEYS

Kidney and urologic diseases are a major area of research of the National Institute of Arthritis, Metabolism, and Digestive Diseases. The Institute supports many fundamental and clinical studies aimed at broadening our understanding of the functions of the kidneys and improving our ability to prevent, control or cure the various kidney diseases through research grants and contracts awarded to medical centers, universities, and industrial and development organizations across the United States. Reports from this research demonstrate that impressive advances in life-saving knowledge and techniques are resulting from this Federal initiative.

KIDNEY DISEASE RESEARCH

The kidney is the central organ in one of the most complex body systems and has the function of maintaining a stable internal environment through removal of the end products of biochemical processes from the blood and regulation of the body's electrolyte composition and fluid and acid-base balance. The kidney also affects other physiological processes, such as regulation of blood pressure and stimulation of the formation of red blood cells.

Many aspects of the kidneys and of the urinary tract are being studied such as: kidney structure as correlated with function, control of sodium excretion, congenital malformations, drug-induced kidney damage, effects of streptococcal host infections and of disorders of immunity on renal tissues, subcellular reactions to injury in the kidney, vitamin metabolism, chronic renal disease, and its complications such as renal osteodystrophy (uremic bone disease).

Three kidney disease groups - infectious, hypersensitive, and hypertensive - account for about three-quarters of all renal deaths. To achieve a reduction in the number of these deaths, better methods of preventive treatment, intensified case-finding and more effective, prompt therapy and, above all, greater understanding of the basic causes and mechanisms of disease are essential. While supportive measures for end-stage kidney disease, such as dialysis or transplantation, are life-saving and life-extending, the most desirable objective of research is, of course, control and prevention.

The Calciuretic Effect of Dietary Protein

Since 1920 several different investigators have observed that the addition of meat or other protein source to the diet causes an increase in urinary calcium in man. In recent research, NIAMDD grantee Dr.

Sheldon Margen and associates at the University of California were the first investigators to use well-controlled formula diets in an attempt to make a critical evaluation of the effect of protein intake on urinary calcium excretion (calciuria).

A markedly positive correlation was found between the amount of protein ingestion and the degree of calciuria. Increasing the daily protein intake from 0 to 90 grams resulted in an approximate 800 percent increase in calcium excretion, irrespective of calcium intake. This effect of protein intake occurred in all the various studies conducted and was also observed with administration of pure L-amino acid mixtures. The data clearly demonstrate that urinary calcium is directly related to protein intake but four other minerals studied (magnesium, sodium, potassium and phosphorus) are not. The investigators report that the mechanism of this calciuretic effect of protein is as yet unclear.

Chronic Kidney Failure

The therapeutic value of administration of keto-analogues of the essential amino acids to patients with chronic renal failure and clarification of the mechanisms by which these compounds act is being studied by Dr. Mackenzie Walser and associates, grantees working at Johns Hopkins University. Goals of the investigations include the exploration of long-term keto-acid therapy in patients with the disease and the development of keto-acids for intravenous use. Thus far, the investigators have established that the keto-analogues of five essential amino acids, valine, leucine, isoleucine, methionine and phenylalanine, when administered along with the four remaining essential amino acids, lysine, threonine, tryptophan and histidine, diminish urea nitrogen appearance and make nitrogen balance more positive or less negative in patients with chronic renal failure. The investigators have also shown that hydroxy-analogues of isoleucine, methionine, and phenylalanine can substitute for the corresponding amino acids in the diet in rats. Since the hydroxy form is more stable, less expensive and more palatable than keto-acids, the investigators have initiated studies with these analogues in patients with chronic renal failure to determine the efficacy of these compounds in reducing urea production and accumulation.

Further benefits of these studies include a better understanding of how nitrogen is transferred between organs and how external nitrogen losses might be modified, which may lead to a better understanding of dietary essential amino acid measurements and to a possibility of reducing the patient's daily protein requirement.

Selective Renal Vein Sampling in Hypertension

Detection of surgically correctable kidney damage has been improved by a study showing that selective renal vein sampling in hypertensive patients with segmental renal lesions can identify and localize such sources of renin. The study was conducted by NIAMDD grantee Dr. Edward G. Biglieri and associates at the University of California.

Renin, a proteolytic enzyme produced by the kidney, is involved intimately in the pathogenesis of an important type of hypertension. Whenever a kidney, or a segment thereof, is deprived of an adequate supply of oxygen, renin is released from the oxygen-starved renal tissue and enters the general circulation where it causes, indirectly, a generalized increase in blood pressure. A comparison of bilateral renal vein renin levels is of value in evaluating hypertensive patients who may have unilateral renal ischemia; sampling of the main renal vein would be of little use, however, in assessing the importance of the occasional lesion which affects only a segment of one kidney.

The investigators recently demonstrated that selective sampling of venous drainage from such isolated lesions is both technically feasible and diagnostically rewarding. They now have shown that selective renal vein renin sampling can specifically identify a localized source of renin that may be overlooked by main renal vein sampling and, thus, can facilitate detection of patients with surgically correctable lesions. The technique should improve the diagnostic value of renin measurements in patients with segmental renal lesions, particularly since remedial surgery can reduce elevated blood pressure in 90 percent of such patients.

Urinary Tract Stones

The study of kidney stone formation is an area which deserves increasing investigative activity, Dr.Charles Y. Pak and associates at the University of Texas Southwestern Medical School postulate that calcium oxalate crystals are critical for the formation of most stones. These investigators are studying the growth and structure of these crystals in different media in the presence of various additives, such as sodium pyrophosphate, sodium tripolyphosphate, magnesium nitrate, creatine, and urea. Their findings indicate that these additives aid the dissolution of calcium oxalate crystals.

In another study, Dr. pak and his associates working with Dr. Frederick C. Bartter of the National Heart and Lung Institute report that they controlled the hypercalciuria and recurrent renal stone disease associated with calcium hyperabsorption by means of a low calcium diet and daily administration of cellulose phosphate. The treatment was well tolerated and no serious side-effects were observed.

Cellulose phosphate is known to have a high affinity for calcium, is nonabsorbable, and is only slightly hydrolyzed in the gastrointestinal tract. The investigators say it apparently acts by binding dietary calcium in the tract, thereby decreasing its absorption into the circulation, and thus its subsequent urinary excretion. Although this blood calcium-lowering effect might stimulate parathyroid hormone (PTH) secretion, neither blood PTH concentrations nor bone density changed significantly during treatment. Moreover, because it is not absorbed, cellulose phosphate administration was not associated with soft-tissue calcification.

This study indicates that, in patients with increased intestinal absorption of calcium, hypercalciuria may be corrected and calcium renal stone formation prevented by a low-calcium diet and decreased intestinal calcium absorption secondary to calcium binding by cellulose phosphate.

Electron Probe Microanalysis

Electron probe microanalysis for analysis of the ionic composition (sodium, potassium, calcium, magnesium, chloride, phosphate and sulfate) of glomerular ultrafiltrate and proximal and distal tubular fluid samples is being applied in a few grantee laboratories conducting investigations of the kidney. The advantages of the system are its specificity for many ions which are presently difficult to identify, the minute (picomolar) samples needed and the preservation of the sample following analysis. With this technique, data may be obtained to give insight into transport mechanisms by comparison of the electrolyte composition of tubular cells to that of tubular fluid content. It is also anticipated that these methods can be applied to the study of processing and locating drugs within the kidney and other organs.

ADVANCES IN KIDNEY TRANSPLANTATION

Several of the National Institutes of Health support research aimed at improving organ transplantation procedures. The NIAMDD has been the principal supporter of research in kidney transplantation. The kidney is the organ most frequently transplanted, and to date over 15,000 kidney transplantations have been performed throughout the world. Depending on the selection of the donor organ and how close donor and recipient tissue types are matched, between 45 and 85 percent of kidney transplants remain functional after two years. Some recipients (a special class: patients who have received kidneys from an identical twin) are now in their second decade since receiving a kidney transplant.

In patients with chronic progressive kidney failure, emergence of the end-stage syndrome of uremia may be delayed by using special diets. Subsequent to this stage, artificial kidneys are widely used and may allow patients to live relatively normal lives. In many cases, a kidney transplant permits a more natural existence, although drug treatment to prevent immunologic rejection of the kidney must be continued indefinitely in all cases except those involving organ transplants between identical twins. Complications from the continued use of immunosuppressive drugs are frequent.

Transplant rejection is an obstacle to the routine use of kidney transplantation, and research continues to focus on the search for drugs that suppress the body's immunologic mechanisms, and on improved immunologic matching of donor kidneys with suitable recipients. Preservation of cadaver kidneys for proper matching with a suitable recipient has improved, and the problems of preserving kidneys for distant recipients have diminished in recent years, although improvements in methods of preservation still are needed.

Organ Preservation

A cadaver kidney prior to transplantation preserved at 25°C for one hour has less than 25 percent chance of survival due to progressive damage during this period of "warm ischemia." Although drugs such as methylprednisolone and phenoxybenzamine have been used to protect such kidneys, and all such kidneys are now quickly cooled and preserved through cold storage with or without pulsatile perfusion using special supercooled solutions, about one in ten must be discarded because of resultant tissue damage.

Recent research by NIAMDD grantee Dr. John S. Najarian and Dr. Luis H. Toledo-Pereyra of the University of Minnesota has shown that allopurinol, an anti-gout drug, enhances tissue and organ survival during hypoxia. They have shown that allopurinol protects dog kidneys from the deleterious effects of warm ischemia during preservation, and that it may have potential clinical value in organ preservation for transplantation. Based upon their results in animal research, the investigators currently are planning clinical trials of human kidneys.

Matching HL-A Antigens and Transplant Survival

For some time scientists have been investigating the possibility that a patient's chances of success with kidney transplantation can be enhanced by matching of HL-A antigens of his blood with that of the donor. This has been found to be true when the donor and recipient are from the same family, and workers are continuing studies to determine whether such matching significantly improves the survival of kidney transplants between people who are not related. Institute grantee Dr. F. O. Belzer and associates at the University of California, however, recently reported a study in which they analyzed 200 unrelated cadaver kidney grafts and found no correlation between graft survival and degree of closeness of HL-A matching. The investigators state that the results of their study indicate that cadaver kidneys may be transplanted even if the recipients are poorly matched for HL-A antigens.

ARTIFICIAL KIDNEY - CHRONIC UREMIA PROGRAM

It is estimated that about 60,000 patients annually suffer irreversible, fatal kidney failure. This damage may be caused by primary kidney diseases such as glomerulonephritis, by longstanding high blood pressure or kidney infection, kidney stones, advanced diabetes or longstanding and neglected hypertrophy of the prostate gland. Among those who succumb to end-stage kidney disease each year, over 10,000 are considered suitable candidates for maintenance dialysis.

Among those patients who are treated on dialysis, many experience a number of undesirable complications, and the cost of providing this kind of therapy continues to be high. Kidney transplantation is a possible alternative, but many patients cannot withstand major surgery, and even those who do undergo transplantation must be sustained on dialysis until a proper donor organ is located. After surgery the patient may again receive dialysis if the new kidney does not function properly at first or is subsequently rejected. There is one more important function of

artificial kidneys: they are used as a means of life-maintaining support in cases of acute kidney failure, as well as in the treatment of a moribund patient with accidental or suicidal drug over dosage. In these settings the use of dialysis may be decisive in the outcome.

Since its organization in 1966, the goals of the Artificial Kidney - Chronic Uremia Program of the Institute have been to bring about improvements in artificial kidney apparatus and methodologies. Optimal development of new, better dialysis apparatus and methods is still hampered by incomplete knowledge concerning the specific nature of uremic toxicants. For this reason, research into the fundamental aspect of the toxic nature of uremia and basic and clinical studies of the long-term effects of uremia and of dialysis treatment are essential.

About 70 research and development projects are supported by contracts with universities and nonprofit and industrial research laboratories to give a broad approach to problems of highest priority. These include clinical trials of more efficient or less costly dialyzers, development of special adsorbents for uremic toxins, studies to elucidate the nature of the aberrant metabolic changes in uremia, and the maintenance of a national registry of all patients who are being treated with dialysis. The Program is also funding studies aimed at isolation and identification of toxic factors which must be removed from the patient's blood, in addition to metabolic wastes and other substances that accumulate during kidney failure. Many projects are directed at pathophysiology of uremia in an effort to prevent or control complications.

Much has been achieved in the past few years. Clinicians now have an adequate -- though not optimal -- mode of dialysis based on treatment three times each week, usually lasting six hours. Peritoneal dialysis, a method of filtering impurities from the blood utilizing the lining of the abdominal cavity, or peritoneum, and its blood supply as a dialyzing cavity, is at a stage that it can now be utilized for chronic maintenance therapy either in the home or in an institutional setting. Investigators have learned a great deal about how to deal with and possibly avoid osteodystrophy (uremic bone disease) associated with long-term dialysis, but this and other medical complications still pose serious problems.

Research and development in this field must focus on achieving dialytic therapy which would be provided to the patient on a daily basis, or alternate-day basis, for relatively short periods, and which could be self-administered when conditions are suitable. In very preliminary trials, portable dialysis equipment is now being tested which would allow patients to perform their own dialysis treatment away from the home or dialysis centers. A high priority for future improvement involves long-term, well-controlled, multiclinic studies to compare the effects on clinical well-being of short-term daily dialysis and long-term periodic dialysis.

A conspicuous impediment to daily dialysis is the imperfect interface between man and machine which now exists. In some treatment facilities, patients are using a single needle device in conjunction with A-V fistulas (subcutaneous, surgically constructed connections between an artery and a vein) for abbreviated daily dialysis. This may be an important advance toward a better method of coupling the human circulation to an extracorporeal dialyzing device.

Another important goal is to improve dialyzer design so as to lower the hours of dialysis from the accepted 18 hours per week to 10 to 12 hours or less. This can be done by increasing the filtering surface area of dialyzers or through the introduction of more permeable dialysis membranes.

Scientists must also focus on the prevention of known complications of long-term dialysis, namely renal osteodystrophy, anemia, peripheral neuropathy, and premature cardiovascular death. Data from the National Dialysis Registry show that the leading cause of death in long-term dialysis is heart disease followed by strokes. Strong emphasis must be placed on studies of alterations in patterns of fat and carbohydrate metabolism which occur during the course of long-term dialysis since these conditions are suspected of being causally related to premature degenerative changes in blood vessels. Another area where studies must be focused is preventing anemia.

New Ultrafiltration Cell

Scientists at the University of Pennsylvania, supported by a contract from the Artificial Kidney Program, recently developed an ultrafiltration cell to remove excess sodium and water efficiently, rapidly, and inexpensively from fluid-overloaded patients on chronic hemodialysis. The device, which can be used in series with an artificial kidney or as a separate unit, may enable physicians to treat more rapidly and efficiently patients with edema secondary to cardiac failure with acute pulmonary edema. Current treatment of edema, regardless of its cause, employs low-sodium diets and diuretic medication. Treatment usually requires days to weeks, while a few unresponsive patients may require salt and water removal with peritoneal dialysis or the artificial kidney.

In treatment with the new device, arterial blood is delivered to the ultrafilter by a blood pump, filtered and measured and returned to the patient. This therapy is simpler and safer than fluid removal by peritoneal dialysis or hemodialysis. No serious complications, such as clotting (which is prevented through use of an anticoagulant) occurred in over 100 trials. The investigators suggest this therapy could logically be extended to patients with chronic congestive heart failure or pulmonary edema, and would conceivably replace costly and prolonged hospitalization with one or two relatively brief ultrafiltration treatments.

New Prosthetic Arteriovenous Shunt Available

A new implantable, compact prosthetic arteriovenous blood access shunt, developed and tested by Institute grantee Dr. T. J. Buselmeier and associates at the University of Minnesota, has now been made available commercially. The new shunt offers several advantages over standard shunts and passages, notably faster blood flow and less clotting and very few complications. Because of its shorter length and decreased resistance, the device allows three times faster blood flow than the standard Quinton-Scribner shunt. The faster flow prevents blood sludging and clotting, decreases the incidence of infection and trauma, and provides for prolonged shunt survival. The new shunt has been implanted in many patients previously unable to maintain functional standard shunts. Its commercial availability represents an important advance in the technology of hemodialysis.

Clinical Control of Renal Osteodystrophy

Many of the patients maintained with repeated dialysis suffer from uremic osteodystrophy, the characteristic bone demineralization which weakens the skeleton and makes it prone to fractures. In many cases, excess calcium and phosphate liberated from the skeleton may be deposited in soft tissues in the joints, the eye, and even heart muscle. Bone weakening is the end result of a combination of factors. The progressive decrease of kidney function allows excessive phosphate to be retained in the body at the same time that impaired vitamin D activity prevents adequate intestinal absorption of dietary calcium. In an effort to increase calcium blood levels to normal, the parathyroid gland secretes excessive amounts of parathyroid hormone, which in turn causes a mobilization calcium and phosphate from the bone to compensate for low blood calcium of levels.

In research previously reported, an Institute grantee demonstrated that vitamin D is not biologically active in the body, but a tertiary derivative of this vitamin is highly active. Vitamin D is converted in the liver to 25-hydroxy vitamin D3 and then by the kidney to the highly active form - 1,25-dihydroxy vitamin D3 (1,25-DHCC). The actions of the vitamin were evaluated recently by NIAMDD grantee Dr. Anthony W. Norman and associates of the University of California. The investigators studied the biologic response of normal and uremic subjects to 1,25-DHCC, and found that minute quantities produced a substantial increase in intestinal calcium absorption in the normal subjects. Much larger doses were required to augment calcium absorption and correct "vitamin D resistance" in patients with advanced renal failure, observations compatible with defective renal production of the metabolite in such patients. These studies provide support for the opinion that 1,25-DHCC production is impaired in uremic patients. They also furnish insight into normal requirements for the vitamin D metabolite and offer a point of reference for its effects in various disease states.

In other research, Institute grantee Dr. James M. Burnell and associates at the University of Washington performed bone biopsies of normal patients and those with renal osteodystrophy and found evidence that the progression of renal osteodystrophy is associated with decreased

carbonate content in areas of osteomalacic lesions or osteofibrosis. The investigators report that their data appear to identify the existence of a bone "maturational defect" previously found only in rodents. They found a decrease in bone carbonate and an increase in magnesium. The investigators suggest that more research would be necessary to determine whether this may be ascribed to the hyperparathyroidism which characteristically afflicts patients with chronic renal failure.

It has been shown by other investigators that overactivity of the parathyroid gland and calcium abnormalities can be partially avoided in dialyzed patients by restriction of phosphate intake. This is done by adding phosphate-absorbing substances to the diet. It has also been found that elevation of the calcium concentration in the dialysis bath will obtain higher calcium blood levels and counteract the tendency for secondary hyperparathyroidism. A combination of both phosphate restriction and blood calcium increase, if started early enough, has been shown to be effective in preventing the bone dystrophy of chronic renal failure.

Accelerated Atherosclerosis in Prolonged Maintenance Hemodialysis

Evidence has been accumulating in recent years to suggest that cardiovascular disease is the leading cause of death among patients undergoing chronic hemodialysis therapy. Institute grantee Dr. Belding H. Scribner and associates at the University of Washington have obtained evidence in a retrospective study of 39 patients on prolonged hemodialysis that accelerated atherosclerosis is a major risk. The study revealed a mortality rate of 59 percent, with 14 of 23 deaths resulting from atherosclerotic complications; myocardial infarction was responsible for eight deaths, strokes for three, and refractory congestive heart failure for three. The incidence of these complications was many times higher than for non-uremic, normal and hypertensive groups of comparable age, and similar to rates found in Type II hyperlipoproteinemia (an inherited condition of having excess lipoproteins in the blood which characteristically lead to early atherosclerosis and cardio vascular impairment). The data suggest that the probability of dying from such complications increases with time on dialysis, and that dialysis candidates with symptomatic cardiovascular disease probably should not receive chronic hemodialysis. At the same tiem, they note, such life-prolonging therapy cannot be denied by the fear of potential vascular complications, inasmuch as ongoing research may ultimately result in proper control of the etiologic factors involved in accelerated vascular disease.

The Hematologic Effect of Androgen in Uremic Patients

Several NIAMDD grantees have shown in recent studies that the androgenic hormones, testosterone and fluoxymesterone, can improve the anemia associated with chronic renal failure in patients who are on maintenance dialysis. Further studies are needed, however, to determine whether patients without kidneys are as responsive to androgen therapy as are those who have not undergone nephrectomy.

Research by Institute grantee Dr. Walter Fried and his associates at the University of Illinois Medical Center has shown that anemia becomes more severe, and more resistant to androgen (testosterone)

therapy, after the kidneys are removed, as evidenced by packed cell volume and erythropoietin responses. These studies support the clinical impression that nephrectomy should be delayed as long as possible in patients with chronic renal failure who are undergoing maintenance dialysis. The researchers say their findings indicate that androgens stimulate erythropoiesis largely by increasing the amount of erythropoietin produced by kidney remnants even after the excretory function of such remnants has ceased.

Conferences, Publications, and Scientific Communication

Symposia and workshops on critical problems and opportunities in kidney disease research are organized regularly by NIAMDD or co-sponsored with a particular university research center. In 1974, the Institute organized or co-sponsored symposia on the following subjects: 1) Treatment of the diabetic end-stage kidney disease patient, 2) Endocrine functions of the kidney, 3) Adequacy of dialysis treatment (and how to assess and improve it), and 4) Novel therapeutic approaches to uremia. These conferences were attended by several hundred research workers and practitioners in the respective fields. The proceedings were published in prestigious scientific journals and distributed to a readership of several thousand.

Each year, also, the Institute brings together the research contractors of the Artificial Kidney program with staff and consultants for a comprehensive meeting at which all ongoing work is reported and discussed. Extensive illustrated proceedings, describing the most recent advances, are subsequently published and widely distributed to interested research workers and practitioners in the field of dialysis.

For years, the Institute has published, on a quarterly basis, a current-awareness publication, Artificial Kidney Bibliography. This publication provides bibliographic citations of the latest research findings from throughout the world (regardless of language of original publication) in the field of end-stage kidney disease treatment. This very popular publication is now being enlarged into a new, comprehensive publication, Kidney Disease and Nephrology Bibliography which will appear regularly every two months and will cover the entire field of kidney disease and research related to the kidney and urinary tract.

The Institute also distributes to individuals and concerned groups pamphlets descriptive of kidney disease, dialysis, and kidney transplantation, and responds to inquiries on specific related topics.

National Dialysis Registry

Data gathered by the National Dialysis Registry, organized and maintained by the Institute's Artificial Kidney Program, now covers about 85-90 percent of the individuals receiving dialysis treatment in the United States. Since its implementation in mid-1969 the Registry has accumulated data on approximately 16,500 people treated in more than 400 dialysis programs throughout the country. Currently, the Registry data indicate that over 13,000 patients are now being treated by chronic intermittent dialysis. The data currently collected includes that necessary for patient identification and primarily demographic information, including location of the treatment, type of dialysis, age, sex, and reason for discharge

from dialysis treatment. If death is the reason for discharge, the immediate cause of death and underlying conditions are also recorded. Another item of information which the Registry began collecting this year is the clinical diagnosis for kidney failure if it is known, and this information is now available on approximately 3,400 patients.

Registry data on mortality taken from death certificates indicates that heart disease remains the most prevalent primary cause of death. Other data show that since 1970 the dialysis patient population for the country as a whole has grown from 24.4 patients per million population to over 55 per million. This means that the number of persons being treated in dialysis programs has more than doubled over the last four years.

OUTLOOK

Research conducted and supported by the National Institute of Arthritis Metabolism, and Digestive Diseases has contributed much to the understanding and treatment of kidney disease. Now through the recent funding of a study, Evaluation of Research needs in Nephrology and Urology, in which over 90 clinical and basic scientists in the field are participating, the program to reduce kidney disease should gain new impetus. The objectives are to assess current research in kidney and urinary tract disease, define the needs for future research in these areas, evaluate the feasibility of carrying out significant research, establish priorities for approach to the various needs that are identified and to present the results to the scientific and lay community.

National Institutes of Health
National Institute of Arthritis, Metabolism, and Digestive Diseases

NUTRITION

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) bears the principal responsibility for medically oriented nutrition research supported by the Federal Government. In addition to direct research activities in its laboratories and clinics in Bethesda, the Institute supports nutrition research projects through grants to research centers throughout the United States and abroad. These activities cover the full spectrum of nutrition research, from fundamental metabolic and physiologic studies, to programs designed to determine how best to alleviate malnutrition and nutritional deficiency diseases.

Obligations for Programs in Nutrition

	1972	1973	1974	1975	1976
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases	$7,887,000	$7,896,000	$8,999,000*	$8,263,000*	$8,276,000

Research Status in Nutrition

The role of nutrition in medicine and health has changed dramatically over the past several decades. With increasing emphasis on the nutritional plight of nations throughout the world, research in thic field is now viewed with an unprecedented sense of urgency. Health problems such as scurvy, beriberi and rickets which no longer menace American people still still plague foreign populations, contributing to ever-rising rates of malnutrition and starvation.

The United States is not exempt from nutritional problems. While malnutrition is not an overt national problem, it is endemic in special population groups and requires strenuous public education efforts coupled with economic aid where feasible. Obesity has turned into a major national health problem which afflicts close to one quarter of the adult population and an increasing percentage of children. Thus, at the present time, the health of millions of Americans is impaired by dietary excesses or, in smaller numbers, by a few specific deficiencies.

In light of these facts, nutrition research has become increasingly involved with development of low cost, high quality foods which, it is hoped, will be instrumental in stemming the tide of undernutrition abroad. On the opposite end of the spectrum is research into the causes, management and prevention of obesity, which experts now believe has reached epidemic proportions in the United States. Research has produced a variety of approaches to help obese patients achieve weight loss, including, for extreme cases, total starvation and intestinal bypass surgery as well as weight reduction by behavior modification. A significant Institute accomplishment of the past year was the establishment of an Obesity Center at St. Luke's Hospital, affiliated with the Medical School of Columbia University, New York, for the multidisciplinary treatment of this problem.

* Includes $383,000 in 1974 and $67,000 in 1975 from restorations of 1973 impounded funds.

Investigators are now examining the role of trace elements such as zinc, iron, chromium, silicon, fluorine and others, to determine their essentiality to health. Also under study are numerous vitamins, their roles in proper growth and development, and the consequences and correction of deficiences.

The study of nutrition continues with the enthusiasm that marked its first advances - the discovery of vitamins and nutrition-deficiency diseases fifty years ago. Investigations this past year have added to our knowledge base of human nutrition in health and disease, and also have indicated extensive need for research in chronic nutritional disorders.

Scope of Research

The research grants program of the NIAMDD is divided into two classifications - the biochemistry and physiology of normal nutrition, and nutritional disorders. Projects in the physiologic processes of normal nutrition involve study of body composition, digestion and absorption of nutrients in the gastrointestinal tract; appetite regulation and food intake, biochemistry and physiological role of nutrients and their fate in the body, quantitative requirements for proteins and amino acids, carbohydrates, fats and fatty acids, minerals, trace elements, vitamins, and fluids and electrolytes, interrelationships between different nutrients and between nutrients and hormones, and nutrients and enzymes, and the relationship of the intestinal flora to nutrition.

Research in abnormal nutrition involves discovery and definition of deficiency states, nutrient toxicity, obesity, malabsorption of specific nutrients, and investigation of the relationship of diet to specific disease entities, such as celiac disease. Other research relates to nutrition in specific diseases or stress states, such as in diabetes, bone and joint disease, endocrine and immune disorders, gastrointestinal and infectious diseases, inborn errors of metabolism, liver and kidney disease, anemia, skin disorders, and stress (including surgery, trauma, wound healing and environmental extremes).

Excess of Vitamin C Destroys Vitamin B_{12} in Food

Research by NIAMDD grantee Dr. Victor Herbert and associate Dr. Elizabeth Jacob has demonstrated that pharmacologic doses of vitamin C destroy substantial amounts of vitamin B_{12} contained in food.

Earlier studies had shown that vitamin C exerts a destructive effect on crystalline vitamin B_{12}. More recent observations revealed low serum vitamin B_{12} levels in some patients taking 1 gram (gm.) of vitamin C daily.

The Columbia University investigators now report that high doses of C destroy large amounts of B_{12} when ingested in food. To mimic human consumption, meals with a moderate (cottage cheese) and high (beef liver) vitamin B_{12} content were homogenized, incubated after addition of varying amounts of vitamin C, then assayed for B_{12} content.

The level of the modest B_{12} meal was decreased 43 percent by 0.1 gm, 81 percent by 0.25 gm and 95 percent by 0.5 gm vitamin C. By contrast, 0.1 gm vitamin C has a minimal effect on the content of the high B_{12} meal, while 0.25 gm destroyed 25 percent of the B_{12} and 0.5 gm destroyed almost 50 percent. It has been reported that iron stabilizes vitamin B_{12} activity in liver extracts; thus, in the present study, beef liver iron apparently reduced the damaging effect of vitamin C on B_{12}.

These findings lengthen the list of possible adverse effects of large doses of vitamin C, a current popular home remedy for the prevention and treatment of the common cold. The report concludes that daily ingestion of 0.5 gm or more without regular evaluation of vitamin B_{12} status is unwise and may result in vitamin B_{12} deficiency anemia.

Metabolic Studies in Skylab Orbital Flights

A scientist of the National Institute of Arthritis, Metabolism and Digestive Diseases has described significant in-flight losses of calcium, nitrogen and phosphorus from bones and muscle of Skylab astronauts as a result of living without gravitational stress. This suggests that prolonged space flights of many months duration could endanger the human musculoskeletal system unless effective protective measures can be developed.

Studies of all participants in the three Skylab flights of 28, 60 and 84 days, respectively, called for rigorous feeding and waste collection regimens. These required fairly constant dietary intake, continuous 24-hour urine collections and total fecal collections for 21 to 31 days before each flight, throughout each flight, and for 17 to 18 days after each flight, for a total of 909 man-days of metabolic study.

Although total urinary calcium losses were moderate in relation to the whole skeleton, over a period of many months such losses could endanger the strength of critical areas of the body's long bones. Similarly, the increased losses of urinary nitrogen and phosphorus reflected substantial loss of muscle tissue which could be clearly observed in the astronauts' legs. Mineral and nitrogen balances returned to normal after the astronauts returned to earth.

Investigators Dr. G. Donald Whedon, NIAMDD, and associates at the Veterans Administration Hospital, Sepulveda, California, and the NASA-Johnson Space Center, Houston, concluded that although prolonged space flight of 6 to 9 months might reasonably be predicted as "safe," an 18- to 36-month trip (the time required to go to Mars and return) could have serious effects on bone and muscle unless protective measures can be developed.

The Calciuretic Effect of Dietary Protein

NIAMDD grantee Dr. Sheldon Margen and associates have demonstrated that urinary calcium excretion in man is directly related to the amount of intake of protein or amino acid mixtures.

Since 1920, several investigators have observed that the addition of meat or other protein source to the diet causes an increase in urinary calcium in man. The present study, however, is the first to use well-controlled formula diets in an attempt to make a critical evaluation of the effect of protein intake on urinary calcium excretion (calciuria).

The University of California, Berkeley, researchers found a markedly positive correlation between protein ingestion and calciuria. Varying protein intake of up to 90 grams (gm) of nitrogen per day resulted in an approximate 800 percent increase in calcium excretion, irrespective of level of calcium intake. This effect of protein occurred in all the various studies conducted and was also observed when amino acid mixtures replaced the protein.

These data clearly demonstrate that urinary calcium is directly related to protein intake and, among five minerals studied (calcium, magnesium, sodium, potassium and phosphorus), this relationship is unique for urinary calcium. The mechanism, however, of this calciuretic effect of protein is as yet unclear.

Anorectic Substances in Urine

Anorectic substances (agents which diminish appetite) are vaguely defined materials of great interest to nutritionists because of their effects on regulation of food intake. Recently, Institute grantees at the University of Hawaii obtained from rat urine substances which, when administered in the pure form, caused significant depression of both food intake and weight gain.

Isolated by Drs. Y. Lee and I.J. Lichton, the most effective fraction appeared to be a protein with a molecular weight of 30,000 to 50,000. Further exploration of its chemical structure, mode of action, and significance in relation to the physiological control of food intake may open new approaches to the problem of obesity and related disorders.

I.V. Solutions Result in Infant Fatty Acid Deficiency

Recent research by a grantee of the NIAMDD and the National Heart and Lung Institute demonstrates need for the addition of lipids to intravenous feeding solutions for young infants. The findings support the contention that these solutions must be complete in all nutrients necessary for normal infantile growth.

Studies by Dr. Ralph Holman of the Hormel Institute in Austin, Minnesota, showed that in seven infants under six months of age for whom intravenous alimentation was required, there was biochemical evidence of essential fatty acid deficiency within days of initiation of the fat-free parenteral regimen. Subsequent feeding of small oral doses of methyl linoleate slightly altered fatty acid patterns toward normal, but was not as effective as oral feeding of a normal formula diet.

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Similar findings in related studies point to the conclusion that lipids should be a required part of intravenous nutrient solutions to avoid essential fatty acid deficiency in infants if these solutions are the sole source of nutrition for any length of time.

Bypass Surgery: Protein Nutrition and the Liver

Studies by grantee Dr. Thomas Pozefsky and colleagues have provided evidence to link the liver dysfunction associated with jejunoileal bypass surgery for extreme obesity with surgery-induced protein malnutrition.

Liver dysfunction, marked by striking fat accumulation and occasional cirrhosis, is potentially the most serious complication of jejunoileal bypass surgery for intractable, massive obesity. Comparable hepatic changes occur in protein deficiency states such as kwashiorkor (protein-calorie malnutrition), suggesting that protein malnutrition may be of an important origin in the liver disease of obese persons after bypass surgery.

Assessment of liver cell studies and function, and protein nutrition in 18 such patients now has revealed that shortly after bypass surgery, when weight loss is rapid, liver dysfunction and marked fatty degeneration are found simultaneously with a significant decrease in blood levels of most essential and nonessential amino acids. When weight stabilized, amino acid concentrations tended to return toward normal. Oral amino acid tolerance tests suggested that improved intestinal absorption accounted for the enhanced amino acid blood profiles. This in turn, suggests that early postoperative amino acid supplementation may be of value in preventing liver disease.

The Johns Hopkins University investigators postulate that liver fat accumulation during rapid weight loss is causally related to surgery-induced protein malnutrition, and its diminution upon weight stabilization is a reflection of gradually improving amino acid absorption.

Metabolic Defect Causes Hereditary Vitamin D-Dependent Rickets

Investigators at the University of Wisconsin have reported evidence that hereditary vitamin D-dependent rickets is caused by a genetically determined block in renal vitamin D metabolism.

Hereditary vitamin D-dependent rickets, a disorder causing abnormal bone development, is one of the ten known vitamin D-refractory (unresponsive to treatment) syndromes. Unlike the other nine, however, its treatment with very large doses of vitamin D brings about complete remission of the disease. To date, no convincing evidence has been presented for defective vitamin D metabolism in any of the other refractory conditions.

Previous research had shown that vitamin D_3 (which is biologically inactive) is converted in the liver to 25-OHD_3 and then in the kidney to a more active metabolite 1a,25-$(OH)_2D_3$ which possesses full biologic vitamin D activity. In the current study, Dr. Hector F. DeLuca and associates have obtained data indicating that vitamin D-dependent rickets is an inborn error of vitamin D metabolism characterized by defective kidney synthesis of 1a,25-$(OH)_2D_3$.

Clinical studies were conducted to ascertain the relative doses of the various metabolites of vitamin D required to reverse the disease's effects. As expected, massive doses of vitamins D_2, D_3 and 25-OHD_3 were necessary to heal the lesions. By contrast, a minute dose of $1a,25\text{-(OH)}_2D_3$ promptly initiated healing. It is therefore likely that hereditary vitamin D-dependent rickets results from a genetic impairment of the activity of the enzyme responsible for production of $1a,25\text{-(OH)}_2D_3$ in the kidney.

Active Vitamin D_3 in Normal Man and Patients with Kidney Failure

In recent research, a grantee of the NIAMDD has evaluated the biologic response of normal and uremic subjects to $1a,25\text{-(OH)}_2D_3$, the most active form of vitamin D, because of its potential value in treating calcium metabolism disorders which accompany long-term kidney insufficiency.

Vitamin D is converted in the liver to 25-hydroxy vitamin D_3 and then in the kidney to the biologically most active form, $1a,25\text{-(OH)}_2D_3$. Because of its potential therapeutic value, the actions of the vitamin have been evaluated in normal subjects and in patients with advanced kidney failure in whom derangements in calcium metabolism and skeletal calcium stability have been attributed, in part, to its deficient production.

In studies by Dr. Anthony W. Norman and associates at the University of California, Riverside, minute quantities of $1a,25\text{-(OH)}_2D_3$ produced a substantial increase in intestinal calcium absorption in normal subjects. Much larger doses were required to augment calcium absorption and correct "vitamin D resistance" in patients with advanced kidney failure, observations compatible with defective renal production of the metabolite in such patients.

These studies emphasize the regulation of production of $1a,25\text{-(OH)}_2D_3$ from its precursors in normal subjects, and provide support for the opinion that $1a,25\text{-(OH)}_2D_3$ production is impaired in patients with uremic or kidney patients. Also, the findings furnish insight into normal requirements for the vitamin D metabolite and offer a point of reference for its effects in various disease states.

Special Nutrition Research Studies

Specific research projects, carried out abroad among populations with nutritional deficiency diseases, are designed to find solutions to complex malnutrition problems. These projects are largely funded through the U.S. - Japan Cooperative Medical Sciences Program and through Public Law 480 foreign currency program, U.S. -owned local currencies in developing countries derived from the sale of surplus agricultural commodities. Only half of the earth's population maintains an adequate diet, indicating a critical need for research to find ways and means to transform marginal nutrition and overt nutritional deficiency to adequacy.

Traditionally, the Institute has conducted nutrition research in developing countries because of the availability of large population groups afflicted with specific nutritional deficiencies which can be

readily studied. The results from such research are two-fold: it may stimulate emergence to self-sufficiency from mere subsistence in Southeast Asian countries, and may also add knowledge of normal nutrition and nutritional deficiencies that will benefit the U.S. population.

The startling realization that malnutrition does, in fact, also exist within our own population lends an element of expediency to nutrition research. By providing scientific know-how for effective utilization of economical, indigenous protein sources, these programs also discourage dependency of developing countries on the United States for expensive protein-rich foods and enable them to make inroads against endemic protein malnutrition.

Southeastern Asia

The mission of the malnutrition segment of NIH's U.S.-Japan Cooperative Medical Sciences Program is to support both basic and applied research aimed at practical solutions to nutrition-related problems in the countries of South East Asia and other nations in the Pacific area.

The substantial grant and contract program already has brought about significant findings which will help to improve the protein level of rice, the principal food of 60 percent of mankind. Ordinary commercial rice lacks sufficient protein for normal growth and development of children maintained on a predominantly rice diet, and does not protect the adult population from serious protein undernutrition.

Research identified approximately 100 rare rice varieties which contain from 13 to 17 percent protein in contrast to the conventional level of 7 1/2 percent in currently available commercial rice varieties. A vigorous plant breeding program has been started with the aim to develop a variety of high-protein rice which has all the necessary additional qualities (such as disease resistance, high yield per acre, identical taste and mouth-feel as conventional rice) which would make possible and commercially feasible large-scale planting and distribution of high-protein rice.

In the future, however, because of a change in the protocols of the U.S. - Japan program, the agricultural portion will no longer be supported by NIH funds. While the human nutrition aspects of this project will continue under the auspices of NIAMDD, the International Rice Research Institute has assumed the responsibility for agricultural experimentation.

Studies of the distribution, importance and methods of control or elimination of natural toxic substances in legumes and other plant foods focused primarily on the distribution of mycotoxin in the food supply of Asian countries and its relation to human disease. The principal work, supported by a contract with Drs. Gerald Wogan and Ronald Shank of the Massachusetts Institute of Technology, has now been concluded. Their studies resulted in the publication of 15 scientific papers documenting the widespread occurrence of aflatoxin and other mold toxins in Asian foods and their probable association with liver damage in those who habitually consume foods contaminated with such toxins.

In the area of malnutrition and mental development, Dr. Adolpho Chavez and associates of Mexico City have documented the nutritional, sociological, psychological and environmental factors surrounding their subjects to determine their influence on physical and mental development. At the end of three years, the investigators have been able to demonstrate that mothers given food supplements produce more milk, maintaining a plateau for at least 24 weeks after delivery. Significantly, the physical activity of the children who received supplements was higher and became increasingly apparent after the first year, becoming six-fold that of the unsupplemented group by two years of age. Furthermore, the unsupplemented group showed a 20-week retardation in neurological development in the lower extremities and had lower scores in language ability. Both groups suffered a similar number of infections, but the total number of days of illness and the severity of the infections were significantly higher in the unsupplemented group.

The investment in a large nutritional research center in Chiang Mai, Thailand, has yielded a significant amount of data in two priority areas of the US-Japan Program, nutritional anemia, and interactions of malnutrition and infections. In studies by Center personnel, almost 80 percent of the more than 1500 children attending the hospital's out-patient department were found to be iron-deficient and responded completely to iron therapy. In a companion study, 3,230 pregnant women were surveyed for hematologic status: 70 percent were iron-deficient; 20 percent folic acid-deficient; and 13 percent had combined deficiencies. Of particular interest was one case of pernicious anemia discovered during the study--the first reported in a Thai.

The latest study reported from Chiang Mai explored the role of varying amounts of protein and calories on the hematologic responsiveness of children with protein-calorie malnutrition (PCM). In this investigation, the addition of protein and calories elicited a therapeutic response, with protein recording the greater effect. Part of this action is thought to be related to the responsiveness of erythropoietin (a glycoprotein considered to be the humoral plasma factor that stimulates red cell production in the bone marrow) to protein feeding.

In other studies of malnutrition and infection, Dr. Leonardo Mata of The Institute of Nutrition of Central America and Panama has documented the high incidence of bacterial and viral infections, and infectious diseases of all types in children living under conditions characteristic of developing countries, including malnutrition. Dr. Mata's graphic demonstration of the association between frequency of infections in preschoolers and their impaired physical growth and development led him to conclude that weight at birth is the best predictor of child survival. Only 2 of 81 infants weighing at least 2750 grams at birth died within the first six months, and no deaths were recorded among babies weighing 3000 grams or more. Survival rates decreased sharply with lower birth weights.

Because these deaths were mainly from diarrheal or respiratory disease, they were attributed largely to decreased resistance to infection. There

was evidence that the effect on the fetus of the mother's malnutrition during pregnancy was mediated through a higher frequency of intrauterine infections, as judged by levels of immunoglobulins in blood samples taken from the infants at birth.

These observations have awakened widespread interest in the relationship between maternal nutrition and infant birth weight with subsequent morbidity, mortality, and physical growth, as influenced by the interactions of malnutrition with infection in mother and child.

Protein Malnutrition Studies in India

NIAMDD sponsors a vital research and development project in India, funded by Public Law-480 U.S. surplus commodity funds, to study protein malnutrition, intermediary metabolism and selected metabolic disturbances in kwashiorkor (protein malnutrition) patients.

Studies at the Christian Medical College in Vellore include fortification of wheat with lysine, the first, most limiting amino acid in the nutritionally incomplete wheat protein. During a six-month experimental period, children on a lysine-supplemented wheat diet grew significantly in height compared to the children in a control group not given the supplement. This investigation represents the first conclusive clinical finding that lysine fortification of wheat protein, when it is the only source of dietary protein, can significantly improve the growth of preschool children. It also demonstrated the potential benefit of an inexpensive method of improving protein nutrition that is not dependent on educating a population toward better nutrition (a slow procedure at best), or on changing local dietary habits.

In related research, an NIAMDD-supported project at the Central Food Technological Research Institute in Mysore involved laboratory development of food supplements based on inexpensive, indigenous protein sources to prevent kwashiorkor prevalent among preschool children in India. This research led to development of Miltone, a protein-rich product combining buffalo or cow milk with a solution of peanut protein isolate, which has the potential of doubling the available milk supply. Other studies demonstrated that many native cereal foods fortified with peanut flour acquired a significantly higher biological value and could serve as a nutritionally adequate, inexpensive source of food for growing children.

Bladder Stone Disease in Thailand

Bladder stone disease is one of the most serious health problems in northern Thailand, occurring primarily among village children five years of age and under. Research by NIAMDD grantees Drs. Aree Valyasevi and Sakorn Dhanamitta indicates that oxalcrystalluria (excessive amounts of crystalline oxalic acid salts in the urine) was commonly found in village urine samples, but only rarely in specimens of city-dwellers. Moreover, calcium oxalate was shown to be one of the main constituents of the urinary stones.

A dietary survey showed that the villagers consumed daily several kinds of local vegetables and leaves of forest plants not eaten by the townspeople. Further study revealed that these food items such as tampala and bamboo shoots were high in oxalic acid content, leading to the heavy oxalcrystalluria and crystal clumping, particularly among children.

To counteract this occurence, the investigators at Ramathibodi Hospital in Bangkok administered oral doses of orthophosphate which eliminated almost all crystalluria and crystal clumping in the patients studied.

The researchers concluded that in all future studies on the origin of bladder stone disease, external sources of oxalic acid (which heretofore had not received as much attention as the possibility of metabolic abnormalities) should be an important consideration.

Outlook

Improved methods of evaluating nutritional adequacy have contributed to a new emphasis on the definition and diagnosis of malnutrition. Evaluation of nutritional status is no longer dependent on ill-defined symptoms or on the subjective judgment of the examining physician.

The investigations this past year have proven productive in adding to our knowledge base of human nutrition in health and disease, and have also indicated new areas for much-needed research in chronic nutritional disorders. The Institute is anticipating more significant advances in these research efforts in the coming years.

Dr. WHEDON. Arthritis and rheumatism are terms that refer respectively to inflammation and destruction of joints and to disease affecting tissue surrounding the joints. This group of diseases is of major concern to us, since it inflicts much suffering and disability and also has a serious adverse effect on the economy.

The question with regard to the causation of the most crippling of these disorders, rheumatoid arthritis, remains a fascinating as well as a challenging enigma. Does an inappropriate reaction of body tissues to an apparently foreign material produce the chronic state of the disease, and if so, what is the basis for the primary disturbance? Is it, perhaps, of infectious origin?

Mr. FLOOD. Do you mean viral or what?

Dr. WHEDON. Viral and possibly of some bacterial agent of an unusual sort. These possibilities have been in the wind for a long time, and nothing has been proven solidly, but we are developing some new evidence supportive of this possibility.

Mr. FLOOD. You know I have asked this question of some medics whom I have known a long time, you ask them a question about arthritis and they look at me as though I have been drinking or something. These are older fellows.

Mr. WHEDON. Of course, there is an acute form of arthritis which used to be common caused by a number of bacteria, notably gonococcus arthritis. That, of course, is less frequent than it used to be.

Mr. FLOOD. Why is that?

Dr. WHEDON. Because of the effect of the antibiotic drugs.

Dr. LAMONT-HAVERS. We are seeing a recurrence of infectious arthritis because it is not entirely wiped out. But now we see a recurrence.

Dr. WHEDON. The discussion we were having was really, on rheumatoid arthritis, the crippling type. There have been suggestions of an infectious origin but no solid evidence has been forthcoming.

Lending credence to this hypothesis are several recent studies of a body protein known as histocompatibility antigen W27, a tissue component which can stimulate a specific antibody response by the body's immune system in individuals with such arthritis-like diseases as ankylosing spondylitis and Reiter's disease. Grant-supported investigators have now found evidence of a prevalence of this same antigen in patients with juvenile rheumatoid arthritis, thus suggesting a common increased susceptibility to a causative agent, possibly of an infectious nature.

RHEUMATOID ARTHRITIS

Mr. FLOOD. You are suggesting arthritis is not a condition of advanced age, it is more common but not exclusive?

Dr. WHEDON. Particularly with regard to rheumatoid arthritis there is no particular association with advancing age.

Mr. FLOOD. All right, you go ahead.

Dr. WHEDON. This new lead on the kind of disordered immune reaction in rheumatoid arthritis will be closely pursued.

A more optimistic picture is emerging in the treatment of the various forms of arthritis and bone disease. Our grant-supported investigators have produced fresh evidence of the value of gold salts in the long-term treatment of rheumatoid arthritis, resulting in significant decreases in pain and in signs of inflammation.

Mr. FLOOD. What do you mean by gold salts?

Dr. WHEDON. Just what it says. Salts of the metal gold. There has been variable enthusiasm for them in the past, partly subdued because of significant side effects in some patients; what we have obtained is a study which shows that if these compounds are given over a longer period of time for something like 4 or 5 months, week after week, then continued less frequently for up to a couple of years, they are more effective apparently, than they have been under previous systems of treatment.

Our investigators are also continuing their research on knee joint replacement with implanted prostheses, following their earlier successes in the hip with this form of corrective orthopedic surgery for severe deformity from osteoarthritis.

DIABETES AND OTHER METABOLIC DISEASES

Diabetes remains a serious and complicated disorder of metabolism despite the fact that we have at our disposal methods of management of the disease for millions of patients. It ranks sixth on the list of diseases causing death in the United States; its complications include enhanced atherosclerosis and consequent heart disease and circulatory disease in the extremities, as well as nerve damage, kidney failure and blindness. For juvenile diabetics on insulin therapy, these complications may develop at an early age. It is extremely important to explore ways to suppress development of these long-term complications, and we are also concerned that research be pursued on the basic roots of the disease which involve aberrant carbohydrate and fat metabolism, as well as altered action of the sugar-regulating hormones, insulin, glucagon, and newly discovered products of the pituitary gland.

Our research next year will also cover studies of transplantation of the insulin-producing beta cells of the pancreas which we hope may ultimately provide improved diabetic control. This procedure, however, has only been successful thus far in animals of the same genetic strain. Such research in human beings is regarded as highly experimental if not premature, because of serious problems of tissue incompatibility, and further extensive animal research must be conducted.

Further, on the important subject of diabetes, this committee will recall that several years ago we reported on an intensive, long-term investigation by 12 leading medical centers known as the UGDP—university group diabetes program—study of the efficacy and safety of two oral antidiabetic drugs. It was the consensus of the investigating group that these drugs were no more effective than diet alone in treating adult-onset diabetes, and the data further suggested hazard to life from such drugs from possible premature cardiac death. Now these data have been reviewed by a blue-ribbon panel of independent biomedical statisticians of international reputation who recently published their findings in the Journal of the American Medical Association. This review study generally upheld the original conclusion of potental danger of death from heart attack, and which—as Newsweek recently and I believe correctly put it—recommends the drugs only as a treatment of "last choice"—one to be used only for adult onset diabetic patients whose disease cannot be handled by dietary control or insulin.

On a more positive note, I am happy to report that we hope to expand our support of diabetes-endocrinology research centers. These are interdisciplinary research efforts, for which we provide core resources and research support funds to investigators from a number of departments who will coordinate their varied investigations of diabetes.

CYSTIC FIBROSIS

In the meantime, we are pursuing our research on a number of other metabolic diseases, including cystic fibrosis, a grave familial disease of children and young adults. One of the most hazardous complications of cystic fibrosis is chronic obstructive lung disease. In the past, our investigators in Bethesda have demonstrated that cystic fibrosis patients exhibit a decrease in the rate of mucus clearance from the airways due to impairment of the normal sweeping motion of the hairlike cilia which line the respiratory tract.

MUCUS

Mr. FLOOD. What is mucus?

Dr. WHEDON. The semiliquid, gummy, sticky material secreted all the time from the glands of the mouth, the trachea, the air tubes in the lungs and also all of the inner "tubes" of the body such as the intestines.

Mr. FLOOD. Why do the glands do that?

Dr. WHEDON. Really as a protective system, particularly in the lungs. Whenever we breathe, we take in foreign matter of all kinds, bacteria and foreign particles. Having this wet material secreted constantly and having these hairlike cilia sweep the liquid up and out to one's mouth is a way of getting rid of these foreign materials. The patient with cystic fibrosis has some inherent, apparently genetically determined, defect so that his mucus instead of being thin and easily managed, is thick, sticks together, may actually obstruct the airways and parts of the lungs and makes an ideal situation for infection to to take place and bronchial pneumonia. This is the way most patients with cystic fibrosis get into serious lung trouble and eventually die.

Our scientists have now shown that a pharmacologic agent, terbutaline, increases the mobility rate and clearance of mucus and may thus have significant therapeutic value.

I might interrupt myself, Mr. Chairman, to say in the past there has been very close attention to this therapeutic aspect of cystic fibrosis. The use of washing, or lavage, with a saline solution spray and certain special positions of the body have been used to try to improve the extrusion of foreign material. These patients require a great deal of hospital care and home care by their parents, so to find an agent which will liquify, loosen up the secretions is a very substantial aid in this very serious disease.

HEMATOLOGY

Many Americans are afflicted with the killing and disabling blood disorders, including blood clotting diseases such as hemophilia, and the anemias, such as Cooley's anemia. Studies of diseases of the blood constitute an important part of the research program of this Institute in coordination with the National Heart and Lung Institute, with whom we are joined in a new initiative on Cooley's anemia. This Institute's particular effort is support by contract of an intensive search for new iron-chelating agents which could prevent the ultimately fatal buildup of iron in the tissues and organs of patients who must be kept alive with the aid of repeated blood transfusions.

DIGESTIVE DISEASES

The list of disorders of the digestive system is immense, afflicting millions of Americans each year. These chronic and disabling diseases, including peptic ulcer, ulcerative colitis, and other disorders of the pancreas, gallbladder and liver, are also complex disorders, both from the viewpoint of the practicing physician and from that of the biomedical researcher.

Last year I reported to this committee that our grant-supported investigators had shown in preliminary animal trials that metiamide, a histamine and blocking analog agent, may be of value in reducing gastric acid secretion, and may thus represent a physiological approach to peptic ulcer control. Now our grantee-scientists have demonstrated in preliminary clinical trials the effectiveness of metiamide in blocking gastric acid secretion in man. Since a transient adverse side effect has been observed in a few patients in Great Britain, however, with this compound, we are actively pursuing the search for related agents with a similar action but which would be devoid of undesirable toxic effects.

If I may interrupt myself again, I might say that another similar compound has been found and is under study, so we have hope we may get around this undesirable toxic effect of metiamide, although it is not highly toxic; the number of side effects have been limited.

We have launched a major research attack on peptic ulcers by establishing a Peptic Ulcer Center in Los Angeles to be operated jointly by the UCLA School of Medicine and the Veterans Administration Wadsworth Hospital Center. A 5-year study has been undertaken, involving 10 key investigators with multidisciplinary expertise who will study peptic ulcer from various approaches.

NUTRITION

Nutrition research is one of the oldest programs of the Institute and we continue to bear the principal responsibility for medically oriented nutrition research supported by the Federal Government. Our program ranges from basic metabolic and physiologic studies to obesity and malnutrition, two problems of wide concern in this country and abroad. We expect during this next year to give particular attention to obesity, a condition widespread in the United States which carries a high predisposition to diabetes, high blood pressure and liver and gallbladder disease.

UROLOGIC AND KIDNEY DISEASES

The statistics associated with urologic and kidney diseases are staggering, inasmuch as more than 8 million Americans suffer from diseases of the urinary tract, while some 60,000 die annually of irreversible kidney failure. We support many studies which seek to provide new knowledge with which to control, prevent, or cure the varied kidney diseases. At the same time, we are making a major effort to extend the development of kidney transplantation and dialysis with artificial kidneys into more physiologic, and individually predictable, therapies for those patients with irreversible kidney disease who face a downhill path to fatal uremia. Our contract-supported scientists have developed

a device to help overcome a problem associated with maintenance of a patient on an artificial kidney, that of removing excess fluid. The researchers have found that a newly developed ultrafiltration cell removes excess sodium and water efficiently, rapidly, and inexpensively from fluid-overloaded patients on chronic hemodialysis.

Although used thus far only in a dialysis setting, the new treatment can conceivably be employed in such fluid-overload conditions as chronic congestive heart failure, in lieu of currently used procedures which call for costly, prolonged hospitalization.

DERMATOLOGIC DISORDERS

Disorders of the skin include psoriasis, a disfiguring disease which numbers as its victims some 4 million Americans. The total number of persons afflicted with psoriasis and other dermatologic problems is large, and personal suffering is of great magnitude.

In psoriasis, therapeutic management has been generally unsatisfactory and certain drugs with a therapeutic potential have, also, unfortunately, caused serious side effects. Now, however, our grant-supported scientists have reported clearing of skin lesions in a significant number of patients who were given an oral dose of a photoactive drug, methoxsalen, and were subsequently exposed to ultraviolet light of a special long-wave length. Although this type of interaction of light and drug, "photochemotherapy," is not a permanent cure for psoriasis, it appears to clear the skin lesions effectively and its repeated use seems to be well tolerated by the psoriatic patients who have been treated thus far. This method of management of psoriasis however, has been tried for only a short time so far and it will now be subjected to intensive, controlled investigation for long-term effectiveness versus late toxicity, which is always of great concern in a new treatment which looks so promising at the start.

In conclusion, Mr. Chairman, the budget request for the Institute for 1976 is $148,409,000. I shall be pleased to try to answer any questions and supply additional information desired for the record.

ALLOCATION OF RESOURCES

Mr. FLOOD. It appears, Doctor, you have a considerably larger spectrum of diseases than probably any of the other Institutes out at NIH. However, despite all that, your budget looks no different than all the others. A reduction of about 14 percent. That is $24 million. What is the impact of that reduction? What areas in your shop are hardest hit?

Dr. WHEDON. With this degree of reduction, there is really no area that can escape. We have to spread this impact over all the areas of our operation.

Mr. FLOOD. No privileged regions?

Dr. WHEDON. We have some areas to which we are going to attempt to give special attention; namely, diabetes and arthritis, kidney diseases, and digestive diseases. With this situation, we obviously have an overall reduction in our effort.

Mr. FLOOD. For instance, in your research career programs on page 182 of your justifications, there you are cutting the research pro-

grams to 83 in 1976, why is that program being cut back? Are you just trying to save money or what?

Dr. WHEDON. In the overall budgetary situation, choices have to be made as to how we will best use our funds. This program has to share in that situation.

RESEARCH GRANT SUPPORT

Mr. FLOOD. Will you be able to fulfill all your commitments in 1976?

Dr. WHEDON. We expect to carry out through the commitments of grants we have made but we shall be able to make no new awards next year.

Mr. FLOOD. On page 160 of those world-shattering documents that we get, called budget justifications, you show you are going to award $7 million in new grants in 1976. Are those going to be projects which have never received any Federal support?

Dr. WHEDON. That is correct. This is the way we have set up our budget so that we will assign $7,200,000 for new applications for new work.

Mr. FLOOD. You have a reduction of $24 million.

Dr. WHEDON. That is correct.

Mr. FLOOD. Where did you get the $7 million for new grants, did you have that hidden under a rug or did Charlie Miller bring it up in a bag or what?

Dr. WHEDON. What we have done, Mr. Chairman, is attempt to spread the funds which we are requesting among the various mechanisms of support. If you would look at the top line of that table, you will see that the funds set up for noncompeting regular grants amount to $81 million. Now, with this amount of funding in that category, we shall not be able to follow through on all of the commitments which we are making in this fiscal year. We shall have to make some choices next year with regard to continuation of some of these grants.

NONCOMPETING RESEARCH GRANT

Mr. FLOOD. Go over to page 171 of your justifications. You show $20,841,000 in low priority grants awarded in 1975 as a result of the failure of the rescission request whose moral commitment will not be funded.

Is that why you did not use the $7 million we were just talking about a few minutes ago, to offset a part of that reduction for the noncompeting grants? What did you do? These budget people, we know them better than you do.

Mr. MILLER. I want to repeat something which has already been said by Dr. Lamont-Havers and Dr. Cooper. They made it clear we had presented the justifications to you with the same number of new starts as before you took the action on rescissions. Both witnesses have tried to make clear in their opening statements that when we take a look at the final budget results for fiscal 1976 we may have to revise our plans. It could be we will retain some of the new money, but the actual number of new starts now shown in the justification is only a transitional portrait of the situation.

Dr. WHELDON. We will have to make some judgments.

ARTHRITIS AND DIABETES COMMISSIONS

Mr. FLOOD. Every time one of these new institute fellows show up I have to ask the question. I know that campus out there sometimes they do not talk to each other.

What is the status of the Commission on Arthritis, and the National Commission on Diabetes?

Dr. WHEDON. Taking diabetes first, the National Commission on diabetes was established in September, the members were appointed in December, and the first organizational meeting of that committee was held in March.

Mr. FLOOD. When do you think that Commission will publish its report? You know commissions, some are good. What about this outfit?

Dr. WHEDON. The act requires that the Diabetes Commission have its report completed and submitted within 9 months of the time it begins its work, which means about December 1975.

Mr. FLOOD. They certainly have sold this Congress on diabetes.

Dr. WHEDON. This Commission has jumped into its work with great energy. It has planned several meetings and hearings in several cities and intend, I am sure, to make a robust and energetic report.

Mr. FLOOD. When are you going to fully, robustly implement those two acts?

Dr. WHEDON. Well, the Arthritis Act, as well, requires the establishment of a commission which has been set up. It too has had its first organizational meeting, last week. Both commissions are required to compile a long-range plan for the conduct of research programs, for related control and prevention, epidemiologic studies, dissemination of knowledge, and so on, not only for our Institute but for all the institutes which may be involved. In diabetes particularly, there are active programs related to diabetes in seven of the other institutes. This is a sizable job the Commissions have to do. They have to put together a detailed set of recommendations.

RESEARCH AND TRAINING CENTERS

Mr. FLOOD. In your statement, you were talking about the training centers. When are you going to start funding these research and training centers, the ones provided for in the Diabetes Act?

Dr. WHEDON. The centers which are authorized in the Diabetes Act are different, I am sure you understand that, from the five centers we are now supporting which are research centers; the centers in the Act are not only for research but for the training of professional and allied health personnel in techniques and methods related to these diseases. It also provides for the educational side, education for the patient, dissemination of knowledge broadly to the public and for the investigation and testing of new methods of therapy, so-called demonstration projects. The authorization for these projects is extremely broad and as such, these centers will be costly. The specific concept of these centers will be a matter of joint decision between the recommendations of the Commission and its long-range plan and the leadership of the National Institutes of Health and the Public Health Service.

SUPPORT OF COMMISSIONS

Mr. FLOOD. You are making quite a big deal for those two Commissions. How much is in the budget for those two Commissions?

Dr. WHEDON. The monetary support for the work of the Commissions is contained in the total budget of the Institutes.

Mr. FLOOD. Can you tell how much?

Dr. WHEDON. The amount of money we expect to expend—at the present time, we are spending $295,734 for a contract in support of the work of the Diabetes Commission, then there will be additional funds for travel of the Commission and the staff. We are in the process of formulating a contract to support the work of the new Arthritis Commission.

ORAL ANTIDIABETIC DRUGS

Mr. FLOOD. There is a lot of controversy over this drug orinase. What is the problem with that?

Dr. WHEDON. The problem was brought about by the UGDP study. To cut it short, the drug has effects either on cardiac muscle or blood vessel walls or in some way which we do not understand, which indicates that there is a greater likelihood of a diabetic patient on these drugs having a heart attack than if he is not. This was a careful study of over 10 years' time and there has been a recent comprehensive analysis by biostatisticians which confirmed it. They admitted there were deficiencies, but despite these, the overall conclusions that it was hazardous were sound.

ENRICHED FLOUR

Mr. FLOOD. You fellows always come up with something which attracts attention, but last year you got a lot of attention here when you told us there was some interest in increasing the iron level in enriched flour in order to prevent iron-deficiency anemia. Obviously, everybody eats flour and it attracted a lot of attention. You used the word "interest". Has the idea gone beyond the mere word "interest"? Is anything actually being done?

Dr. WHEDON. I will turn to Dr. Burton.

Dr. BURTON. If I may address myself to that, Mr. Chairman. As you remember from last year, there have been serious proposals to triple the amount of enrichment iron to be put in flour and flour products in order to make sure that part of our population not getting enough iron in its diet, namely, the young female teenager and the woman of child-bearing age, would receive enough iron in their diet because it is put into their flour. This almost became a working regulation until, about a year ago, a number of biomedical researchers raised certain questions. They said if you put enough iron into bread according to the new schedule of higher iron fortification, to take care of the needs of the females at risk——

Mr. FLOOD. A lot of publicity came out, enriched bread, they did not mention iron or these hearings, but all of a sudden everybody was being enriched all of a sudden, that is why we thought it all grew out of this thing here. Not any more, they cut it out.

Dr. BURTON. There was concern that males who eat a lot of bread might receive too much iron. Also, there are some people with an

inherited trait toward iron overload who are liable to develop an excess iron-storage condition, called hemochromatosis.

Mr. FLOOD. What happens if you get too much iron?

Dr. BURTON. The normal person would eliminate the excess with his feces but there are about 10,000 people or more with this iron-storage disease. And there are others who have the inherited potential for that same disease and they cannot reject any excess dietary iron.

Dr. WHEDON. The excess iron is stored in the liver and interferes with liver function.

Mr. FLOOD. Please give us the full story for the record.

[The information follows:]

IRON FORTIFICATION OF FLOUR PRODUCTS

The Food and Drug Administration is considering a new regulation that could triple the amount of iron presently being added to enriched white bread and flour. The proposed revision of standards for enriched bread and flour, supported by the American Bakers Association and the Millers' National Federation, would require 40 mg of iron per pound of enriched flour and 25 mg per pound of enriched bread and rolls, about twice the maximum and three times the minimum now permitted.

In support of this proposal it is claimed that there is widespread iron deficiency anemia in the United States and that the iron needs of low income families and of many women of childbearing age cannot be met by the usual diet or by current iron fortification of bread and flour. Those opposing the measure believe that the need for fortification has not been demonstrated and that excessive intake of iron could lead to harmful accumulation of the metal in persons with disorders of iron metabolism and in active adult males with heavy bread consumption. It is also stated that iron deficiency can be treated selectively with medicinal iron salts without increasing the iron intake of the entire population.

The recommended daily allowance of the Food and Nutrition Board of the National Research Council for men is 10 mg. and for women 18 mg of iron. If the iron content of the diet is raised to provide women with their recommended daily allowance, the daily iron intake of males with high calorie consumption will far exceed the recommended amount. Those opposed to adding more iron to flour and bread argue that the recommended daily allowance for women is pegged unnecessarily high.

It is generally assumed that any increase in iron intake leads to a decrease in iron absorption so that harmful amounts of the metal are not accumulated, but some investigators have found that when excessive amounts of iron are ingested, excessive amounts are absorbed, irrespective of need. Information is inadequate on the risks to normal males of long-term ingestion of high dosages of iron; it has been suggested that long-term studies of iron-fortified diets be undertaken to test the effect of the new enrichment schedule on normal individuals. It has also been suggested that studies be carried out to show that fortification of flour at the new schedule is indeed effective, i.e., that the added iron will be absorbed at the expected rate and will lead to an increased hemoglobin content of the blood.

Opponents of iron enrichment at the new high levels have suggested that adding that much iron to the diet might aggravate the disease hemochromatosis, in individuals who have it and would induce it in estimated tens of thousands of individuals who have the inherited trait for the disease but who have not had a chance to develop it because their average diet is not unnecessarily burdened with iron. Hemochromatosis is an iron storage disorder in which patients accumulate enormous quantities of iron in the liver and other tissues because their body cannot reject any extra amounts of iron found in the diet. In their 40's and 50's patients with hemochromatosis develop diabetes mellitus, cirrhosis, and heart failure. Eventually the disease is fatal.

Other scientists have pointed out that increased iron fortification may also be harmful to patients with cirrhosis and other chronic liver diseases. These patients have an increased uptake of iron. It has been estimated that there are 9 million alcoholics in the United States; how many of these have some degree of liver injury is not known.

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Iron overload also occurs with aplastic and other anemias, including thalassemia—Cooley's anemia—and sickle cell disease; patients with such chronic anemias have an increased uptake of iron so that if they are not iron deficient, they absorb more iron than they need. In addition, with current methods of management of Cooley's anemia, patients are periodically given blood transfusions which further increases iron loading. This institute is now supporting, by contract, development of iron chelating agents which when given to patients will remove excess iron from their bodies.

In view of these objections the Food and Drug Administration has so far not implemented the proposed new regulations. Somewhere in between the strong proponents for increased iron fortification of flour and the opponents who feel damage to specific groups of individuals from this measure, there are many scientists on the middle ground who suggest that the recommended increase in the iron content of flour and bread should be delayed, at least until the efficacy of this measure has been actually tested and the safety of iron fortification is studied in normal males and in patients with hemochromatosis, thalassemia, sickle cell anemia and chronic liver disease.

ARTHRITIS CENTERS

Mr. FLOOD. As you know, the regional medical program is being phased out. Under this program there were a number of arthritis centers supported all over the country, do you intend to support those centers in 1976?

Dr. WHEDON. There is no way in which we can provide support for those centers. It is not merely a matter of money, Mr. Chairman, it is a matter of the type of centers. These centers are primarily for the provision of treatment facilities.

Mr. FLOOD. You do not have any money in this budget for the support of these centers?

Dr. WHEDON. No; we do not.

PEPTIC ULCER DRUG

Mr. FLOOD. Last year you told us you were working on this new antihistamine drug which would contribute significantly to peptic ulcer control. What is the situation with that?

Dr. WHEDON. First, studies indicated this drug was quite effective with only minimal toxicity, but there were some patients in a study in Great Britain who showed a depressing effect on their bone marrow.

Mr. FLOOD. You mentioned that in your statement.

Dr. WHEDON. Specifically I did not state what it was. This is a risk to these patients.

ARTIFICIAL KIDNEY PROGRAM

Mr. FLOOD. Last year Dr. Burton told us that one of the aims of the kidney programs is to, of course, make this kidney disease treatment more effective and, of course, less expensive, we hope. What kind of progress are you making in that area?

Dr. WHEDON. We have made steady progress in this respect. There have been some improvements in the kinds of artificial kidneys, the technology of the kidney itself. We are reaching a point now, where we would expect that we can move into dialysis which would take much less time, perhaps 3 hours at a crack instead of 6. This development will be a very substantial improvement and represent a very considerable saving.

Mr. FLOOD. Have you any idea what it costs the social security people to provide this kidney dialysis for those eligible for this under the law? There is a lot of publicity, if you want to get your name in the paper this is the way to do it.

Dr. WHEDON. About $240 million per year.

Mr. FLOOD. We are concerned because we also have jurisdiction over social security, you know.

Dr. WHEDON. They are the ones who administer this and provide the funds for that care. The situation is even more serious because the number of patients who will accede to this form of therapy over succeeding years is going to build up more and more, so that eventually we may have 60,000 patients. We have 16,000 patients, for example, now, and this is going to build up.

Mr. FLOOD. Is that a lot?

Dr. WHEDON. When you realize there are probably 50,000 or 60,000 patients who might be eligible. That is what it is going to grow to and that means the cost will grow as well.

PSORIASIS

Mr. FLOOD. As reported to us last year about this drug azaribine, what is the status of that?

Dr. WHEDON. Azaribine is not as effective as we thought it would be. And on the other hand, it has some side effects. It has just been brought out on the market. I am sure it will be used and will be effective in some patients, but I must say I am not enthusiastic about it.

Mr. FLOOD. The story was a good story.

Dr. WHEDON. I think in a disease such as psoriasis——

Mr. FLOOD. What is psoriasis?

Dr. WHEDON. A disorder of the skin in which there is localized redness and scaling and thickening of the skin which is very unsightly and not uncommon, as there are probably 4 million people who have it. In a disease which has been as troublesome as this, whenever you get a new drug there is a desire to make use of it as best you can.

Mr. FLOOD. What is the basic cause of psoriasis? Does sunburn cause psoriasis?

Dr. WHEDON. Sunburn seems to be helpful.

Mr. FLOOD. You have spoiled my next question. Go ahead.

Dr. WHEDON. We really do not know the cause of psoriasis, we know something about the characteristics of cells of psoriasis. They are rather unusual in that they have a very high turnover, a high rate of growth and development.

Mr. FLOOD. Are they asexually produced?

Dr. WHEDON. Yes. And they are four times more active than those in normal skin. Because of this turnover, it led people to think about using anticancer agents.

Mr. FLOOD. A lot of people think it is a cancer.

Dr. WHEDON. Well, it certainly has certain similarities, although it cannot accurately be so described. We talked about methotrexate, which is effective but highly toxic. We are supporting by a contract, a screening of several anticancer drugs, in hope of finding a drug as effective but less toxic.

ARTHRITIS CENTERS

Mr. FLOOD. As to this business of arthritis, there is so much about this arthritis all the time. You were talking about the National Arthritis Act. You made a point about that. You remember that the National Arthritis Act authorizes the support of these so-called comprehensive arthritis centers. Are not those the same centers formerly supported by the regional medical programs?

Dr. WHEDON. No, Mr. Chairman. They are quite different.

Mr. FLOOD. The reason I asked you is, if that is so, why do you not have something in the budget for them?

Dr. WHEDON. Because they are different.

Mr. FLOOD. That takes care of them?

Dr. WHEDON. The centers supported by regional medical programs were primarily for patient care and some investigation of treatment methods. Whereas, the centers in the Arthritis Act are much more broad.

Mr. FLOOD. Some of us are impressed by the work done by the good RMP's.

Dr. WHEDON. I think if I could just say, Mr. Chairman, I think the intent of the language in the act——

Mr. FLOOD. I was trying to get into the back door if I could.

Dr. WHEDON. What I am trying to say is, I think things will be better. The kinds of centers we are trying to develop will be a better type of center to have than what we previously had under RMPS.

DIABETES

Mr. FLOOD. In that special report on diabetes, that is the one where you said you were going to submit several reports and you submitted a special report on diabetes, in that you said at the rate at which diabetes research is proceeding in recent years, it can be hoped it will act as a deterrent of the onset in predisposed persons and suppression of its severe complications are within the realm of possibility.

Will you explain that statement? You sound like the State Department. Will you explain that statement to the committee?

Dr. WHEDON. This note of considerable optimism——

Mr. FLOOD. What ongoing research do you base that on?

Dr. WHEDON. On several developments, Mr. Chairman, the matter of finding out much more about what diabetes is all about and what causes it. That is basically the reason for our optimism.

Along these lines there is gathering evidence that in some forms of arthritis, particularly in the juvenile type there may be an infectious cause. We reported last year on some studies that shows the barest hint of this. Now in this past year there has been a study which shows a rather close association between juvenile diabetes onset and mumps. They found in an extensive study of boys——

Mr. FLOOD. What causes mumps?

Dr. WHEDON. It is definitely caused by a virus. They found that there was a definite positive association and that the yearly incidence of mumps and diabetes go up and down together but with diabetes following behind at a consistent interval. The curves followed each other with the peaks of a diabetes incidence 4 years behind the peaks of mumps incidence.

Mr. FLOOD. Does the female get mumps?

Dr. WHEDON. Yes.

Mr. FLOOD. Not very often.

Dr. WHEDON. Females also have parotid glands. It is possible also to have mumps of the ovary although that is not a common occurrence.

INCREASE FOR OTHER SERVICES

Mr. FLOOD. On page 173 of your justifications, now all the Institutes have this same thing. You are requesting a 25-percent increase in what you call Other Services. How in the world do you explain this large increase in view of the cuts in all these important things, you are about to break down and cry here this morning about all these things you want to do, and grants, and contracts, and research, and whatnot? Yet you have a 25-percent increase, you would never mention that, if I didn't ask you about it.

You have been cutting all the grants and contracts and all the very important things, the very reason for existence out there. Yet along you come with the other services bill and you want an increase.

Mr. MILLS. This is predominantly associated with the intramural program direction. Over the past few years there has been an increased usage of computers to assist in the research endeavors, those associated with the intramural research. We are not only increasing the number of usages but also the price on that is going up.

Mr. FLOOD. I hope you are not getting trapped in the computer business. I'm on Defense appropriations. The first computers we had were in the Pentagon. The first one I saw was as big as this room and you had to climb ladders to get to them. Now they are as big as this water pitcher. They sell you fellows computers and you buy them with this 25 percent on Saturday. Then the salesman comes Monday and says, they have a new system of computers and those are obsolete.

Mr. MILLS. There will be no purchasing of computers in here. This is strictly buying service on computers.

Mr. FLOOD. All right.

Mr. MILLS. There is also the ancillary equipment going with them. We have also increases in some of our contracts that are for services in support of intramural research. This includes the lab animals and other services we use in the Institute in research.

Mr. FLOOD. Twenty-eight percent.

Mr. Natcher.

COMPREHENSIVE CENTERS

Mr. NATCHER. In answer to one of my chairman's questions you mentioned comprehensive centers. Do we fund them in the budget?

Dr. WHEDON. At the present time we do not. We are funding currently five centers that are strictly for research. This is in diabetes that we were talking about. The Diabetes Act authorizes the establishment of comprehensive centers.

Mr. NATCHER. As far as comprehensive centers in regard to arthritis, are we funding any centers in the budget?

Dr. WHEDON. Again, we are not.

VALUE OF SPECIAL LEGISLATION

Mr. NATCHER. Doctor, I vote for most of these acts that we have before the House. I voted for the National Arthritis Act of 1974, Public Law 93-640. Arthritis, as you know much better than I do, is serious in this country. They bring these bills in and we vote for them. We authorize, then later we have to appropriate the money.

Under this particular act the National Commission on Arthritis and Related Disorders, et cetera, will make a survey of Federal, State and local health programs and activities relating to arthritis and assess the adequacy, technical soundness and coordination of such programs and activities and so on down.

Doctor, we vote for these acts. We pass them. More commissions are set up. From the standpoint of research and study of arthritis generally, has there been any benefit derived from setting up these commissions? Do you report back insofar as Federal, State, and local programs are concerned? What do we get for our money and what have we obtained from all the money appropriated for arthritis and research study?

When you get right down to it, Doctor, how does it help as far as discovery of what causes arthritis and what can be done about it and what has been done?

What about this, Doctor? I vote for these bills. They bring them in and I vote for them. We want relief.

Dr. WHEDON. I think the answer is that these legislative activities should facilitate the movement of what we are doing. It focuses attention on the diseases. It attracts the attention of more investigators to these areas and ought to push forward more effectively the ongoing work that we have conducted now for a long time.

Mr. NATCHER. Now, Doctor, aren't you just saying to me in substance that it is just a method for spending more money?

Isn't that just about what you have said to me, Doctor, just spending more money? What about arthritis? What about causes, cures and research? I know it is an easy way to spend more money, setting up commissions, et cetera.

Dr. WHEDON. As I am sure you know, Mr. Natcher, there are really no funds appropriated in these acts. They are authorizations.

Mr. NATCHER. I understand, but you know what that means. When you authorize, then the money is requested. What are we obtaining for our money?

Dr. WHEDON. The authorizations are limited to certain specific areas in this act. The principal one is for the establishment of arthritis centers. Another authorization is for the establishment of a data bank, a system of better accumulation and analysis of data about arthritis and arthritis patients in all respects. I think actually the funds that are requested for these purposes are relatively modest and not nearly as great as what I trust we will be able to put into our research effort.

ADEQUACY OF PROGRAM AUTHORITY

Mr. NATCHER. I don't recall now, at the time, as far as the National Arthritis Act is concerned, about the report accompanying the bill. Did it show approval or disapproval as far as the National Institute

is concerned or the Secretary of the Department? What do we have as far as this particular act is concerned? Did it originate in your shop or here on the Hill?

Dr. LAMONT-HAVERS. Mr. Natcher, as usual I think the response by the executive branch was the fact that there was opposition to the bill because the Secretary had all the necessary authority, but this is the usual response.

Mr. MILLER. But we do feel strongly, Mr. Natcher, and have, I think, for some time, that the trend toward categorical legislation on individual diseases is unfortunate. Where does it stop? We can have 250 of these, there are so many serious diseases. We have always had section 301 authority which gives us all the authority we need for research and training in the biomedical scenes.

Mr. NATCHER. Even though I voted for this bill, you are coming back around to the major premise that it is just another way of spending more money and really not doing too much about the basic problem. Isn't that what we are doing?

Dr. LAMONT-HAVERS. Mr. Natcher, I think, however, that there is certainly another side, particularly with both the diabetes and the arthritis legislation, as I see it. It is of great importance that they both speak of the concept of a commission. I think that the basic problem that both these pieces of legislation were trying to get at—and this is also one of the concerns of the scientific community—was the feeling, expressed a number of times in the Congress and in the outside community, that there is not sufficient coordination within the Federal Government or knowledge of what goes on in the Federal Government regarding the specific diseases. It is certainly true of diabetes and arthritis. The establishment of the commission and of the interagency committee, which is also prescribed in the act, will go a long way toward establishing that type of coordinating mechanism.

We are exploring how we can do this type of coordination in other areas of NIH responsibility. In the case of arthritis, since I happen to have been more closely involved in that during my past activities, I see this as a great opportunity—not to plan on spending money next year or the year after that, but to lay down some guidelines for the future, the next decade or the next 15 or 20 years, on what could be accomplished in this Nation in relation to arthritis. I think that having established those guidelines that it will then be up to Congress, representing the people, to set the priorities of where money should be spent, there or somewhere else.

ADVANCES IN ARTHRITIS RESEARCH

Mr. NATCHER. Briefly, Doctor, in the last 5 years as far as arthritis is concerned, what advancements have we made, as far as research and discovery of causes is concerned? What can be done about it? In the last 5 years, where are we as far as arthritis is concerned?

Dr. LAMONT-HAVERS. What has happened is that on numerous types of arthritic diseases. I think we have been gaining ground. On rheumatoid arthritis, the most severe type involving both children and adults, we are getting a better concept of juvenile rheumatoid arthritis and what it is. As Mr. Flood said, there has been a great

suspicion since the 1920's that there has been an infectious agent. We have been coming closer to that and expect the work going on in other areas of NIH to be applicable.

In the area of the orthopedic and rehabilitative aspects of arthritis, such things as artificial hips and knees have made a tremendous difference. The ability to make arthritic patents more able to carry on an effective life through these procedures has revolutionized the whole area in the last five or ten years. This has been important. Our ability to handle these patients effectively has been improving.

Dr. WHEDON. I would like to add a couple more examples. The study of the disturbed immune processes in arthritis has led to the development of a number of tests of proteins in the blood which have sharpened up the diagnosis of arthritis tremendously. There has been the introduction of surgical treatment for certain forms called synovectomy, which has turned out to be quite useful. There have been ongoing studies of efficacy of certain inflammatory drugs which have been useful. We have not developed the drugs ourselves, but have supported the studies to show whether or not these drugs are effective.

Finally, in this brief listing, the story on gout is a very striking one. Gout is a form of arthritis, I think, with which everyone is familiar. For all the centuries we have had it, we never understood it until we were able to support studies, some conducted within our Institute in Bethesda, which defined the mechanism of development of this process. They found there was both an increased production of uric acid and also diminished excretion of it. Knowing those fundamental processes of the disease, we were able to apply drugs to correct the situation. So we have drugs that will suppress the increased production of uric acid and drugs to facilitate increased excretion. With this basic knowledge first and then effective therapy, gout is very well controlled today.

Mr. NATCHER. Thank you, Doctor. Thank you, Mr. Chairman.

Mr. FLOOD. This increased use of diuretics, is that part of that?

Dr. WHEDON. No, not really. They are related more to cardiovascular disease.

Mr. FLOOD. Mr. Michel?

COLLABORATION WITH OTHER COUNTRIES

Mr. MICHEL. Dr. Whedon. I note that you refer in the opening of your statement to a U.S.-U.S.S.R. cooperative arthritis program. During our hearings on the various institutes, we have had other references to cooperative programs with the U.S.S.R. Just what kind of programs do they have in this area which will be beneficial to our research?

Dr. WHEDON. Speaking for our own Institute, we are particularly concerned with the U.S.-U.S.S.R. cooperative arthritis program. In Russia, as in our own country, the various arthritides are prevalent and both sides are interested in bringing about a change for the better. Russia, with its multitude of ethnically different populations and with its extremes of climate, could be a valuable partner in such a research collaboration, particularly with regard to the epidemiology of different types of arthritis. We are not restricting ourselves to this approach, however; one of the first studies to be undertaken is a long-term trial of the drug, penicillamine, in rheumatoid arthritis. It was one of our

grantees who first discovered its potential usefulness. This was followed by fairly favorable results in larger scale trials in Britain. At this point both we in the United States and the Russians are ready to follow up with well-controlled long-term trials of the therapeutic usefulness of this drug in chronic rheumatoid arthritis.

Mr. MICHEL. Do any other countries have similar research programs that we could benefit from by mutual cooperation? Is the U.S.S.R. the only foreign country with whom we are making this kind of effort?

Dr. WHEDON. On the contrary, there are several such arrangements by the National Institutes of Health and other countries. Our own Institute has been involved for almost 10 years in a major aspect of the United States-Japan cooperative medical science program—that of malnutrition. Within the framework of this program of mutual cooperation, our Institute has been studying productively multiple aspects of malnutrition and its relation to infection, growth and development, and other factors. The NIH also has programs of much more limited extent with certain European countries, such as France; in this program our Institute is involved in some collaborative studies with French investigators on thyroid disease.

Mr. MICHEL. Previously, how was information on research communicated between the different countries? Have we had access to research findings in the Soviet Union before the initiation of this program?

Dr. WHEDON. In general, research information is exchanged at international scientific meetings and by publication in the international scientific literature. It is of interest that this exchange through personal presentation of scientific papers at specialized scientific meetings and through publication of new findings in the various scientific journals is practically as efficient on an international scale as it is within the boundaries of individual countries. It has to do with the nature of scientific research and of the individuals engaged in it. The motivation to learn the latest and to use it for additional advances is simply built into research workers and into the process of scientific research. The factors which work against a more ready international exchange of scientific information are the difference in languages and, in the more freedom-restricted countries, regulations against travel or foreign visitors.

Our own Institute has made special efforts to learn the latest about relevant research abroad and to distribute this information broadly to our various constituencies of scientists through several "current awareness publications" which we publish regularly. These alerting journals in specialties such as diabetes or gastroenterology bring to the reader bibliographic references or abstracts of papers concerning the latest research findings throughout the world regardless of the original language of publication. This includes research literature from countries like the Soviet Union or Japan.

I should also mention here another important resource for information on ongoing scientific research in Eastern Europe, the journal U.S.S.R. and East Europe Scientific Abstracts. This journal, published by the U.S. Joint Publications Research Service, provides abstracts of the most important scientific papers published in the Eastern European countries.

PRIVATE RESEARCH SUPPORT

Mr. MICHEL. I know there is substantial activity in the private sector with regard to arthritis. What other diseases in your institute have substantial private support and do you have any statistics on the amounts of money we are talking about here?

Dr. WHEDON. Actually even though there is substantial activity by voluntary health organizations with regard to arthritis, diabetes and other disorders, the lion's share of funds for research is provided by the Federal Government, primarily through the NIH. For instance, some voluntary health agencies collect money and provide funds to help defray the cost of patient care, but do not support research. Other voluntary health agencies will support training of specialists in that particular field but not research or patient care. A goodly number of agencies will collect funds to support research in their particular disease area. Usually we are not talking however in terms of many millions of dollars, while the relevant support of research by our Institute would be at that order of magnitude. In general, the second most important factor in funding of research in the private sector, after the Federal Government, is the pharmaceutical industry. Voluntary health agencies and private foundations are next.

COOLEY'S ANEMIA

Mr. MICHEL. You mentioned that the Heart and Lung Institute is working with you in a new initiative on Cooley's anemia. What will be the total spent by the two institutes on this disease?

Dr. WHEDON. We will spend approximately $1,208,000 in 1976 on research focused on Cooley's anemia and the National Heart and Lung Institute will spend approximately $1,325,000. The total for Cooley's anemia in 1976 would, therefore, be $2,533,000.

CYSTIC FIBROSIS

Mr. MICHEL. Cystic fibrosis is also a disease which is being researched by the Heart and Lung Institute. What kind of combined effort do you have in this area? What is the total amount being spent by the two institutes?

Dr. WHEDON. Approximately $2,417,000 has been allocated on programs in cystic fibrosis for 1976. The National Heart and Lung Institute estimates their support in this area will be about $400,000 so that together we will spend about $2.8 million in 1976.

PSORIASIS

Mr. MICHEL. We frequently receive letters from people who suffer from psoriasis, a disease which we know affects a large number of people. I am particularly interested in your report on the new method of treatment which seems very promising. You indicate that it is very new and will now be subjected to considerably more investigation. When you have a possible discovery like this, how long does it take before we begin to release the treatment for public use? During a press conference last December, members of the research team who developed this treatment indicate that it could be commercially available by late 1975. Is this a feasible timetable?

Dr. WHEDON. I would like to state from the outset that the promising new treatment for psoriasis to which you refer, which involves the administration of a drug which is photochemically active in the skin, followed by irradiation with a special long-wave ultraviolet light will not be widely available later this year. There are many good reasons why this should be so. The new treatment must now be studied on a larger scale under well-controlled conditions with a view to establishing its safety and the limits of its effectiveness. Our Institute is involved in the new studies which are now being planned in different parts of the country. The only industrial source of the special type of ultraviolet light needed for this treatment has been very cooperative with efforts to develop this new treatment rationally and carefully. This is reassuring since it avoids a possible situation where large numbers of practitioners unfamiliar with the new method, its limitations or its safety, would immediately begin treatment of large numbers of patients with psoriasis. Under the latter circumstances it is conceivable that a potentially effective therapy would fall into disrepute because its helter-skelter use in untrained hands had caused unnecessary damage to patients.

NEW METHODS OF TREATMENT

Mr. MICHEL. Have you come up with any new methods of treatment for any of the diseases in your Institute which you feel will soon be ready for public use? Is there something we can talk about back home to give encouragement to those suffering from these various ailments?

Dr. WHEDON. In the areas of arthritis and orthopedics, probably the most important new methods of treatment concern the implantation of artificial joints to take the place of those that had been irreparably damaged by chronic osteoarthritis. Good results have been obtained in thousands of patients by implantation of artificial hip joints and at this point efforts are directed toward the development and clinical introduction of man-made joint prostheses for knees, elbows and fingers. Along the lines of your question, I mentioned a number of recent developments in arthritis in response to an earlier question by Mr. Natcher. In the area of gastroenterology you have heard about our studies concerning the dissolution of cholesterol gallstones through the long-term oral administration of the bile acid, chenodeoxycholic acid. We hope to be able to report more about that as time goes by. In my opening statement in connection with cystic fibrosis, I have referred to the drug, terbutaline. Institute investigators have shown that this drug may increase the rate of clearance of mucous from the airways of patients with cystic fibrosis; this, of course, would have significant value in improved control of the infections of the lung which beset patients with cystic fibrosis and are usually their ultimate undoing.

The artificial kidney-chronic uremia program of our Institute continues to improve treatment methodology and artificial kidney devices in the treatment of end-stage kidney disease. The most recent developments promise to make it possible to shorten the currently long time of treatment with artificial kidneys by 50 percent, that is, many patients will need to be treated only three times a week for 3 hours per treatment rather than for 6 hours per treatment.

INTRODUCTION OF NEW DRUGS

Mr. MICHEL. How long does it take from the first breakthrough to actual release of a new drug or treatment? If you found what you thought was a terrific new cure for something next week, when would be the first possible time that such a cure could be released to the public on the average?

Dr. WHEDON. This varies considerably based on the disease and the particular drug and also varies considerably with the type of treatment, whether it is medical or surgical. Permit me to elaborate on this point: The Food and Drug Administration has much-needed regulations which govern the development and eventual large-scale usage of a new drug. This involves progressive steps from the first toxicity studies in animals to eventual well-controlled large-scale studies in man. Only after the drug has been found both safe and effective will it be certified for general use. The timespan which covers this period may vary from 1 to 4 years and, of course, depends very much on the nature of the disease and the drug. It will require comparatively little time to establish that a drug is effective against an acute infection, as compared with testing the effectiveness of a drug against a very slowly developing chronic disease. There are no regulations which cover the introduction of a new surgical treatment and the Food and Drug Administration has no jurisdiction over this type of manipulative therapy. Thus, it is theoretically possible that a new surgical treatment, once it has been shown to be spectacularly effective, can spread relatively quickly. Here, of course, the limiting factors are the time required to train surgeons in the new procedure and the readiness with which fellow surgeons will be willing to accept the new procedure, but there is also the risk that such new procedures may be either harmful or of limited value.

Your question is related to a matter of extreme importance to which we must give increased attention. Do we continue to follow the old, current way of releasing new treatments with fairly careful animal testing but with only minimal trials in patients, only to find out years later that certain drugs are potentially harmful (as in the case of diabetic oral drugs) or not harmful but just ineffective in which case large sums of patients' money will have been wasted, or, do we try to adopt a system of cooperative clinical trials under extremely careful controls for selected, highly promising drugs to test their value and safety for patients before general release? The logic of such a system is clear, for protection of patients and for insuring that they are likely to receive benefit when they lay out money for a medicine, but such cooperative clinical trials are very expensive and someone is sure to make the criticism that the time involved will delay release to the public of a drug anticipated to be useful.

INTERINSTITUTE COORDINATION

Mr. MICHEL. Because your Institute has such a wide span of categorical disease responsibilities, doesn't your research overlap with other Institutes? Have you been successful at coordinating efforts in these fields within our own NIH?

Dr. WHEDON. Over the past several years we have made a concerted effort to communicate both formally and informally with other Insti-

tutes with whom there are some areas of scientific overlap. In the field of intramural research there has never been any problem because at NIH intramural scientists constantly collaborate with each other regardless of their Institute affiliation. A similar spirit and attitude prevails in the extramural area. The best examples of this are the so-called dual assignments of research grant applications: Whenever a research proposal is received at NIH which has elements which could put it within the province of responsibility of two Institutes, it is brought to the attention of both Institutes and is actively discussed by the extramural program officials of both Institutes, once it is approved, until a final decision is made as to which Institute will fund the particular project.

On the administrative side, there are constant budget and program reviews at all levels at NIH to avoid any possible wasteful duplication of effort. The activities of the Inter-Institute Committee on Cooley's anemia are a good example of this. In our own Institute we have an ongoing program of analysis and evaluation which takes into account not only studies funded by us but which also endeavors to remain constantly informed on parallel or related efforts by other Institutes and their findings.

On the other hand, I do believe that we should do better on this matter of interinstitute coordination. The creation by both the Diabetes Act and Arthritis Act of formal coordinating committees should be very useful.

Mr. MICHEL. Thank you.

Mr. FLOOD. Mr. Conte.

ALLOCATION OF RESOURCES

Mr. CONTE. Dr. Whedon, this budget projects a $24 million decrease from 1975. Is this really credible, given your new responsibilities under the National Diabetes Act and the National Arthritis Act? How can you undertake these new responsibilities with less money? Is it your other programs which are going to bear the brunt of this decrease?

Dr. WHEDON. The budget before you represents the proposed 1976 funding levels for our current programs in each of the diseases and diseases and disciplines assigned to this Institute, including arthritis and diabetes. It does not include any estimates for the new activities and programs authorized by the two acts you cite. Under each of these acts, a commission has been established to formulate a long-range plan including budget estimates for each of the Institutes affected by that plan. Both commissions are scheduled to complete their work and present their plans next December. Until those plans have been prepared and the specific program recommendations are defined, any request for funding would be premature and extremely difficult to justify to this committee.

Mr. CONTE. In your justification, reference is made to 310 lower priority competing grants whose moral commitment for future support will not be funded. These awards were made as the result of our refusal to approve your 1975 rescission. In your mind, doesn't that indicate some sort of congressional interest in those 310 grants?

Dr. WHEDON. Yes, sir. It is the Department's position, however, that within the funds expected to be available as proposed by the President,

this alternative is preferable to the elimination of new and competing renewal applications in 1976 which will have significantly better priority scores than those to which you refer.

Mr. CONTE. You said in the justification that the moral commitment for support in the case of those grants will not be funded. Don't you feel an obligation to carry out moral commitments? Presumably those grants were not made until just recently. What will happen to those projects without funding in 1976? Will they just fade away, having assembled research teams and begun preliminary investigations?

Dr. WHEDON. Yes, sir. In the past, we have always honored our moral commitments, this would be the first time we have not. We are not sure at this time exactly what will happen, perhaps these people can submit a new and better grant application which will rate high enough to gain support.

Mr. CONTE. Your justification indicates that there will be more than 400 fewer projects being supported by your institute in 1976 than 1975. Can you attribute this to a decreasing need for research in this area? Basically, what a lot of these questions are getting at, is how do you justify a decrease in support for research into an area which affects so many people and in which there is still so much that needs to be done?

Dr. WHEDON. The 1976 budget before you was originally based on the proposed 1975 rescission level and would have reflected increases over that level. It was not revised after the Congress refused to approve the 1975 rescission. There is no doubt in anyone's mind that more could be done; this budget, however, was of necessity developed within the constraints of the President's total economic strategy.

TRAINING GRANTS

Mr. CONTE. Your justification indicates the elimination of manpower programs except for specialized post-doctoral training. Do you believe that the elimination of predoctoral support will provide you with a sufficient pool of well-trained talent to enter your post-doctoral program? Do you have any evidence to support such a claim?

Dr. WHELDON. Excuse me, sir, but this institute has not supported predoctoral training for many years, although some other institutes have. It is the post-doctoral research training grant program which is being phased out. It remains the administration policy that because of the substantial future income potential of the beneficiaries of this program, they should be expected to support their own professional training. In addition, as a result of the passage of the National Research Training Act, we no longer have authority to make new awards under this program. The National Service Awards program is the new mechanism to provide support for research training.

ARTHRITIS

Mr. CONTE. Dr. Whedon, how many people in this country are affected by arthritis? Would you describe the progress which has been made in arthritis research over the past year?

Dr. WHEDON. Approximately 18 million people are affected by one type or other of arthritis and related rheumatic diseases. Probably the

most spectacular advance in arthritis during recent years involves the expanding introduction of replacement of irreparably damaged arthritic joints with artificial joints which given thousands of arthritic patients a mobility they had lost years ago. More specifically in the past year, in the treatment of rheumatoid arthritis, fresh evidence has been obtained of the value of gold salts in the long-term treatment of this disease in decreasing the extent of the pain and inflamation. With your permission, I would like to refer you to a detailed report on achievements in arthritis research during the past year which I submitted for the record at the beginning of my testimony.

Mr. CONTE. Would you describe the actions which you will undertake in implementing the National Arthritis Act?

Dr. WHEDON. Under the National Arthritis Act of 1974 the Secretary, DHEW, has established the National Commission on Arthritis and related Musculoskeletal Diseases which held its first meeting on April 7, 1975. The Commission is charged with the formulation of a long-range plan, encompassing at least the 15 areas itemized in the act, with specific recomendations for the use and organization of national resources to combat arthritis and with the preparation of budget estimates for each of the Institutes of the National Institutes of Health whose activities are affected by the plan.

The Commission plans a series of meetings to collect data and testimony and is scheduled to report its plan in December 1975.

In addition, the act requires establishment of an Arthritis Coordinating Committee for all Government agencies having arthritis-related activities. This Committee is being established, members invited and the first meeting will probably be held in May.

The staff of the Institute is at work on other sections of the act, notably establishment as soon as possible of the arthritis screening and detection data bank. Another major section, comprehensive arthritis centers, must await recommendations for guide lines from the Arthritis Commission.

Mr. CONTE. When do you think an associate director for arthritis will be appointed?

Dr. WHEDON. We are now recruiting actively for an associate director for arthritis. This includes advertisements in the most relevant scientific journals. To date, we have had very little response to our search, and possibly one of the most limiting factors in the search is the fact that the top salary which we can offer under the present restriction on the salary of Federal executives, is $36,000. Needless to say, physicians in private practice in this and many other specialties earn considerably more than this figure. Nevertheless, we are continuing our search and know that eventually we shall find an individual who is both qualified and motivated to take this position.

DIABETES AND HEART DISEASE

Mr. CONTE. Would you explain the relationship between diabetes and heart disease? What portion of heart disease is diabetes related?

Dr. WHEDON. Among other effects, diabetes causes acceleration of the normal degenerative process in major blood vessels—atheroscle-

rosis. Thus patients with diabetes, either of the brittle, juvenile type or of the more stable maturity onset type, will develop degenerative changes in the blood vessels of their heart depending on the length of time they have had the disease. Consequently patients with diabetes may have coronary heart disease and heart attacks many years before their nondiabetic contemporaries. There are no reliable data on what portion of heart disease is diabetes related; "cause of death" in available statistics is usually taken from the death certificate, and in most cases the certifying physician will simply fill in the words "heart attack" or "heart disease" without going into greater detail. For that reason, the national statistics for heart disease as a cause of death do not distinguish adequately the contributory role which diabetes plays in bringing about heart disease related deaths.

BONE INJURIES

Mr. CONTE. In your orthopedics section, do you deal with bone injuries as well as bone disease? What sorts of research are being done on sports injuries? Could you tell me some recent achievements in orthopedic research?

Dr. WHEDON. Our Institute does not yet have an intramural orthopedic section although we are planning for it at the present time. Our extramural orthopedic program deals both with bone diseases in general and with injuries to bone. Thus our support of the research in orthopedics involves basic research related to bone development, bone growth, and bone function in health and disease as well as with bone fractures, injuries to tendons and joints and their respective treatments. These studies, because of their encompassing nature, also involve sports injuries since they too involve similar outcomes such as fractures of bones, ruptures of tendons and injuries to joints, even though the method in which the injury is obtained is different from other trauma related to jobs or highway accidents. Some of our most recent research achievements in orthopedics deal with acceleration of fracture healing with the aid of weak electric currents applied to the site and with the introduction of artificial joints to replace their natural counterparts whenever they have been injured beyond repair.

ACNE

Mr. CONTE. Does your dermatological research include investigations of acne? Is there a cure? If there is, what is it?

Dr. WHEDON. Investigations of acne are also covered in our extramural dermatology program. Even though acne is not a dangerous or fatal disorder it may be a permanently disfiguring one and as such is responsible for a tremendous toll in terms of social, and emotional, and economic damage. Ordinarily acne is a temporary condition which is self-limited and wanes after the late teens. In some individuals, however, it is present to such an overwhelming extent that it may be permanently disfiguring unless actively treated by a knowledgeable dermatologist. The latter usually employs antibiotics in an effort to combat the local infection and he may even have to resort to minor local surgical manipulation.

COLLABORATION WITH OTHER INSTITUTES

Mr. CONTE. Has there been any institutionalization of collaboration with the other institutes to avoid duplication and encourage the pooling of research findings?

Dr. WHEDON. Over the past several years we have made a concerted effort to communicate both formally and informally with other institutes with whom there are some areas of scientific overlap. In the field of intramural research there has never been any problem because at NIH intramural scientists constantly collaborate with each other regardless of their Institute affiliation. A similar spirit and attitude prevails in the extramural area. The best examples of this are the so-called "dual assignments" of research grant applications: whenever a research proposal is received at NIH which could well fall within the province of responsibility of two institutes, it is brought to the attention of both institutes and is actively discussed by the extramural program officials of both institutes, once it is approved, until a final decision is made which institute will fund the particular project.

On the administrative side, there are constant budget and program reviews at all levels at NIH to avoid any possible wasteful duplication of effort. The activities of the Inter-Institute Committee on Cooley's Anemia are a good example of this. In our own Institute we have an ongoing program of analysis and evaluation which takes into account not only studies funded by us but which also endeavors to remain constantly informed on parallel or related efforts by other institutes and their findings.

With regard to "institutionalization", both the Diabetes Act and Arthritis Act require establishment of coordinating committees among Federal agencies involved in some way in work on these diseases or for their patients. The Diabetes Coordinating Committee has already met and the Arthritis Coordinating Committee will meet within the next month.

Mr. CONTE. Thank you.

Mr. FLOOD. Mr. Patten.

CAUSES OF DIABETES

Mr. PATTEN. What is the cause or causes of the diabetes syndrome?

Dr. WHEDON. To be frank, I wish we knew the precise causes of this disease. We know that the disorder results from a built-in error in the body's metabolism. Individuals affected by this serious disease are predisposed to it by their hereditary background. The most obvious chemical defect in diabetes is the body's inability to metabolize carbohydrates normally. As a result, the diabetic is unable to utilize efficiently the carbohydrates he consumes, that is turn them into heat or energy needed for normal body functioning, or store them in the form of glycogen. Instead, the carbohydrates, converted into glucose, accumulate in blood and tissues and spill over into the urine. Primarily, this occurs because of a diminished activity or availability of insulin, a hormone produced by the pancreas, although many other factors are now known to be involved. Not only may there be an eventual decreased production of insulin, but there may also be initial periods of overproduction of insulin, stimulated by a basic impairment in the

normal activity of this hormone. Moreover, there is a growing belief that a hormone antagonistic in its actions to those of insulin—glucagon—which is produced in abnormally large quantities in diabetes, contributes to the abnormal metabolism and disease picture in this disease. Disturbances in the metabolism of fats and proteins accompany the defect in carbohydrate utilization. Side by side with these basic metabolic disturbances are the many well-known, serious clinical symptoms and pathologic manifestations in the body of the diabetic patient, which involve the large and small blood vessels of the body and underly the many serious complications of diabetes, from premature coronary heart disease through blindness.

COMPLICATIONS OF DIABETES

Mr. PATTEN. Do you know the cause or causes of the sequential complications you described in your special report on Diabetes submitted to the Appropriations Committee:

(*a*) Partial or total blindness.

(*b*) Kidney disease.

(*c*) Vascular degeneration (large and small blood vessels).

(*d*) The breakdown of the peripheral nervous system and rendering the male diabetic impotent.

(*e*) Diabetic mothers bearing 6 times more brain-damaged and malformed children than nondiabetic women.

(*f*) Enhanced incidence of heart disease in women of childbearing age as compared with nondiabetic women.

BLINDNESS

Dr. WHEDON. I will take them one by one. First, partial or total blindness as a result of diabetes. This is a complication which occurs primarily in those patients who have had the more serious, "juvenile" type of diabetes. Impairment of vision and eventual blindness due to diabetes usually develops in such patients when they have had juvenile-onset diabetes for about 10 to 20 years. The rate of progress of this disastrous complication varies with each individual. At first the patient suffers from occasional hemorrhages into the semiliquid center of the eyeball. These hemorrhages will clean up in time but they will recur at more frequent intervals. The basic cause is a unique pathologic proliferation of capillaries in the retina of the eye combined with ballooning out of portions of these new blood vessels which are quite fragile and subject to hemorrhaging. Eventually large areas of the retina of the eye will be destroyed by the scarring which follows each tiny hemorrhage and sometimes the entire retina will be detached and result in total blindness.

KIDNEY FAILURE

The next complication you mentioned is kidney disease. In diabetic patients with disease of long standing a specific type of blood vessel damage develops in the kidney—the so-called diabetic intercapillary glomerulosclerosis. In addition, patients with diabetes are also much more prone to urinary tract and kidney infections than normal in-

dividuals. After many years of progression of the specific diabetic kidney damage aided and abetted by recurring infections, the diabetic patient may eventually become confronted with kidney failure due to the fact that an increasing proportion of his functioning kidney tissue has been destroyed and scarred.

VASCULAR DEGENERATION

Under this heading we are dealing with two distinct processes—one referring to the large blood vessels of the body and the other one to the smallest. In diabetes we witness an abnormal acceleration of the "normal" process of degeneration of major and middlesized blood vessels—so-called atherosclerosis. Because of this accelerated degeneration of major blood vessels the diabetic patient who has had the disease for many years can be subject and usually is subject to danger of premature heart attacks due to obstruction of the blood vessels which feed his heart muscle. Also, this process of atherosclerotic degeneration may narrow the lumen of the blood vessels which supply his extremities—particularly the lower portion of his legs and feet. If this condition progresses rapidly he may lose the blood supply to his toes and eventually to his feet. Gangrene is likely to set in in the affected areas and amputation is necessary to save the patient.

The diabetic blood vessel degeneration as related to the smallest blood vessels in the body, the capillaries, is a different process and is very specific for this disease. As a result, the blood supply to and within certain organs becomes restricted and the function of these organs suffers. The best example is the damage to the retina of the eye and the kidney degeneration which I have mentioned before.

Also, it is believed that a similar impairment of the local blood supply to the nervous system of the body underlies the damage to the peripheral nerves which is characteristic of diabetes. Also, there may be an additional mechanism involved in the diabetic damage to peripheral nerves, namely, abnormal carbohydrate metabolism in special types of cells which provide an insulating cover-like the rubber insulation over an electric wire—is believed to damage these cells. This damage will result in local loss of the "insulation" of peripheral nerves, thus damaging their function. Thus we find in diabetes of long standing that the patient may lose some of the sensory functions in his hands and feet and as the condition progresses, he may even have loss of transmission of motor impulses in his nerves. The male diabetic patient who has had his disease for many years is very likely to develop sexual impotence and we believe, again, that this is a result of degeneration of the nerves which actuate his sex organs.

DIABETIC MOTHERS

Lastly, in answer to your question why diabetic mothers bear children with a high proportion of brain damage or congenital malformation, I would reply that these infants had been subjected on the average to 9 months of a chemically abnormal environment. During their uterine life they had been fed with the aid of blood with an abnormal chemical composition, their mother's, and the delicate developmental process which depends so strongly on a normal environment and nutri-

tion of the fetus has been strongly disturbed. Even if the mother is under good medical supervision and receives insulin injections to control her abnormally high blood sugar levels, these levels tend to fluctuate up and down depending on the timing of the insulin injected and the type of insulin used, and in addition the mother's blood characteristically has an abnormal concentration of glucagon and other hormones. All of this in combination impinges on the delicate cellular controls over the sequential development of the fetus and may result in greater or lesser developmental disturbances.

FEMALE DIABETICS AND HEART DISEASE

Normal women in the childbearing age do not run the same risk of heart disease as their male counterparts at the same age. It is believed that the female hormones which are secreted at high levels between the ages of 14 and 44 exert a protective action against blood vessel degeneration by atherosclerosis. Because of the accelerated blood vessel degeneration which I have mentioned earlier as one of the complications of diabetes, we do not see this normal decreased susceptibility to heart disease in diabetic women during the childbearing age. On the contrary, in general, their susceptibility to heart diseases is greater than that of their normal male counterparts of the same age. We blame the typical accelerated atherogenesis of diabetes for this situation, but, of course, we do not really know the basic cause for this enhanced acceleration.

Mr. PATTEN. Will any of the research therapies you described help any of the diabetics by arresting complications described above?

Dr. WHEDON. Most of the therapies I described in my testimony and in the special report on progress in diabetes research will normalize the diabetic patient's symptoms and will enable him to lead a life which on the surface seems to be near normal. Unfortunately we are not sure whether these therapies will also arrest the development of the long-term complications of the disease and—if they do—to what extent. At our present state of knowledge, it is very doubtful that they provide more than a little, if any, control over these long-term complications.

RECENT RESEARCH ADVANCES

Mr. PATTEN. What NIAMDD accomplishment could be called a "major breakthrough?"

Dr. WHEDON. Out of principle, I am hesitant to call any major research achievement for which this Institute is responsible a "breakthrough" until it has really proven to be something that completely alters the treatment and outlook for a disease. As you know, Mr. Patten, the going in diabetes research during the last few years has been characterized by slow and steady progress and not by major leaps and bounds. Because of the long-term complications of diabetes which I have discussed, I will be very cautious about labeling any new treatment method for the disease a "major breakthrough" unless I am fully convinced that the new control mechanism also affects the further development of these serious complications. Of all the research advances mentioned in our special report I would, perhaps, point out two related ones as of possible significance for the future. One has

to do with our increasing belief that diabetes is a "bihormonal" disease, that not only the lack or impairment of activity of insulin are important in its causation but also the abnormally high production of another hormone which is antagonistic to the normal actions of insulin; namely, the hormone glucagon. In connection with this development grantee researchers have also found in preliminary experiments that a hormone called somatostatin which arises in the lower part of the brain, the hypothalamus, which, incidentally, was recently discovered by other Institute grantees, might some day become an important adjunctive treatment in the control of diabetes. This hormone, somatostatin, inhibits the release of growth hormone from the body's master gland—the pituitary gland. We know that in serious diabetes which causes the above-mentioned complications, the level of growth hormone is abnormally high. We have also learned now that somatostatin also inhibits the release of the insulin antagonistic hormone glucagon from the pancreas—and we know that glucagon is abnormally high in diabetes. Thus it stands to reason that somatostatin might be used to "turn off" some of the hormones which may be involved in fundamental diabetic pathology. Indeed, in preliminary experiments it has been found that when diabetic animals and a few patients, in recent experiments, were given both insulin and somatostatin, their blood glucose levels returned to normal much more quickly than if they merely received their ordinary dose of insulin. Needless to say, all of this well have to be followed up further in many experiments before we can make any additional optimistic statements.

Mr. PATTEN. Thank you very much.

Mr. FLOOD. Thank you, Dr. Whedon.

Dr. WHEDON. Thank you, Mr. Chairman.

Justification of the Budget Estimates

Appropriation Estimate

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES

For expenses necessary to carry out title IV, parts D and I, of the Public Health Service Act with respect to arthritis, rheumatism, metabolic diseases, and digestive diseases, [$173,121,000] *$148,409,000.*

For the "National Institute of Arthritis, Metabolism, and Digestive Diseases" for the period July 1, 1976, through September 30, 1976, $37,102,000. (Department of Health, Education, and Welfare Appropriation Act, 1975; additional authorizing legislation to be proposed for $4,344,000 for fiscal year 1976, and for $2,050,000 for the period July 1, 1976, through September 30, 1976.)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Amounts Available for Obligation

	1975 Estimate 1/	1976
Appropriation	$173,121,000	$148,409,000
Comparative transfers to:		
"Research Resources" (For rhesus monkey supply programs)	-76,000	---
"Office of Director" (Transfer of Institutional Relations Branch from Division of Research Grants)	-65,000	---
Total, obligations	172,980,000	148,409,000

1/ Excludes 1973 restorations in the amount of $81,000.

Summary of Changes

1975 Estimated Obligations	$172,980,000
1976 Estimated Obligations	148,409,000
Net change	-24,571,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Within-grade pay increases	---	---	---	+$212,000
2. Annualization of 1975 pay raise costs in 1976	---	---	---	+198,000
3. Annualization of health benefits increase	---	---	---	+20,000
4. Extra day of pay	---	---	---	+37,000
5. Bureau of employee compensation (BEC) rate increase	---	---	---	+3,000
6. Federal Telecommunications System (FTS) rate increases	---	---	---	+4,000
7. Postage rate increase	---	---	---	+5,000
8. Services and supplies	---	---	---	+273,000
9. NIH program evaluation fund	---	---	---	+352,000
Subtotal	---	---	---	+1,104,000
B. Program:				
1. Research grants:				
a. Noncompeting continuations	---	$74,901,000	---	+25,736,000
b. Competing (new, continuations and supplementals)	---	---	---	+19,209,000
2. Fellowships	---	3,386,000	---	+723,000
Subtotal	---	---	---	+45,668,000
Total, increases	---	---	---	+46,772,000

Summary of Changes -- continued

	1975 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Decreases:				
A. Built-in:				
1. Payment to NIH management fund	---	---	---	-$61,000
Subtotal	---	---	---	-61,000
B. Program:				
1. Research grants:				
a. Noncompeting completed or converted to competing status	---	---	---	-19,085,000
b. Competing completed or converted to noncompeting status	---	---	---	-41,935,000
c. Special programs	---	$6,401,000	---	-754,000
2. Training grants	---	9,088,000	---	-8,853,000
3. Research and development contracts	---	7,405,000	---	-655,000
Subtotal	---	---	---	-71,282,000
Total, decreases	---	---	---	-71,343,000
Total, net change	---	---	---	-24,571,000

Explanation of Changes

Increases:

A. Built-in: The increases will provide: 1. $212,000 for within-grade pay increases ($161,000 in intramural laboratory and clinical research and $51,000 in research management and program services), 2. $198,000 for annualization of 1974 pay raise costs in 1975 ($165,000 in intramural laboratory and clinical research and $33,000 in research management and program services), 3. $20,000 for annualization of increased health benefits costs ($15,000 in intramural laboratory and clinical research and $5,000 in research management and program services), 4. $37,000 for one extra day of pay ($29,000 in intramural laboratory and clinical research and $8,000 in research management and program services), 5. $3,000 for increases in the Bureau of Employee Compensation (BEC) rates in intramural laboratory and clinical research, 6. $4,000 for Federal Telecommunications System (FTS) rate increases in research management and program services, 7. $5,000 for postage rate increases in research management and program services, 8. $273,000 for increased services and supply costs in intramural laboratory and clinical research, and 9. $352,000 for increased contributions to the NIH administered program evaluation fund.

B. Program :

1. Research grants:
   a. The amount of $25,736,000 in noncompeting continuations represents the 142 new and 224 renewal grants made in 1974 and 1975 which will become noncompeting in 1976.

   b. The amount of $19,209,000 in competing research grants reflects: 1) $7,204,000 for 124 new awards; 2) $10,805,000 for 188 competing continuations; and 3) $1,200,000 in supplementals.

2. Fellowships: The increase of $723,000 will provide for 53 additional fellowship awards.

Decreases:

A. Built-in:
1. The decrease of $61,000 for the NIH management fund reflects a reduction of this Institute's proportionate share of the costs of centrally furnished services.

B. Program:

1. Research grants:
   a. The amount of $19,085,000 represents the 476 noncompeting regular research grants that were completed in 1975 or that are being converted to competing status in 1976.

b. Of the amount of $41,935,000, $21,094,000 reflects the completion or conversion of 366 competing grants in 1975 to noncompeting status in 1976. The remaining $20,841,000 reflects approximately 310 lower priority competing grants, awarded in 1975 as a result of the failure of the rescission request, whose moral commitment for future support will not be funded.

c. The decrease of $754,000 includes an increase of $46,000 for increased costs of the existing multi-disciplinary research centers, offset by a decrease of $800,000 which represents the termination of 47 research career development awards.

d. The decrease of $655,000 represents 8 research and development contracts which will not be continued in 1976.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
183	Arthritis, Bone and Skin Diseases.....	---	$25,909,000	---	$21,387,000	---	-$4,522,000
188	Diabetes, Endocrinology and Metabolism.....	---	53,989,000	---	44,333,000	---	-9,656,000
194	Digestive Diseases and Nutrition.....	---	30,750,000	---	24,579,000	---	-6,171,000
198	Kidney Diseases.....	---	21,060,000	---	17,461,000	---	-3,599,000
202	Hematology.....	---	11,408,000	---	9,742,000	---	-1,666,000
204	Intramural Laboratory and Clinical Research.	460	23,998,000	450	24,760,000	-10	+762,000
210	Research Management and Program Services..	106	5,866,000	106	6,147,000	---	+281,000
	Total obligations.....	566	172,980,000	556	148,409,000	-10	-24,571,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	566	556	-10
Full-time equivalent of all other positions	53	57	+4
Average number of all employees	619	621	+2
Personnel compensation:			
Permanent positions	$10,716,000	$10,776,000	+$60,000
Positions other than permanent	564,000	570,000	+6,000
Other personnel compensation	58,000	62,000	+4,000
Subtotal, personnel compensation	11,338,000	11,408,000	+70,000
Personnel benefits	1,247,000	1,255,000	+8,000
Travel and transportation of persons	305,000	280,000	-25,000
Transportation of things	75,000	75,000	---
Rent, communications and utilities	360,000	370,000	+10,000
Printing and reproduction	260,000	270,000	+10,000
Other services	3,687,000	4,608,000	+921,000
Payment to NIH management fund	9,962,000	9,901,000	-61,000
Project contracts	7,405,000	6,750,000	-655,000
Supplies and materials	1,780,000	1,890,000	+110,000
Equipment	850,000	850,000	---
Grants, subsidies and contributions	135,711,000	110,752,000	-24,959,000
Total obligations by object	172,980,000	148,409,000	-24,571,000

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1975 House Report	
1. "An Associate Director for Arthritis should be named as soon as possible...." (Page 30).	1. An Associate Director for Arthritis is in the process of being recruited.
2. "The Committee has learned of new research opportunities in this field [ileitis, colitis and diseases of the intestines and colon], following from the study of cholera in India. The Committee believes that these opportunities should be vigorously exploited." (Page 30).	2. Priority has been given to research projects in this field within the overall digestive diseases programs.
1975 Senate Report	
1. "It is also essential that an Associate Director for Arthritis be appointed...." (Page 49).	1. (See House Report above).
2. "The Committee expects that $1,000,000 will be allocated for the programs and duties of the National Advisory Commission on diabetes out of the Institute's increase." (Page 50).	2. Funds have been set aside to adequately support the National Diabetes Commission.

AUTHORIZING LEGISLATION

Legislation	1976 Authorized	1976 Appropriation requested
Public Health Service Act Section 301--Research and Investigation, in general	Indefinite	$117,120,000 2/
Title IV, Part D--National Institute on Arthritis, Metabolism, and Digestive Diseases	Indefinite	
Title IV, Part D--Diabetes Research and Training Centers	$12,000,000	13,024,000 3/
National Diabetes Mellitus Research and Education Act Section 3--National Commission on Diabetes	1,000,000	
Title IV, Part D--Arthritis Screening, Detection, Prevention and Referral Demonstration Projects; and Data Bank	3,000,000	13,921,000 3/
Title IV, Part D--Comprehensive Arthritis Centers	13,000,000	
National Arthritis Act of 1974 Section 3--National Commission on Arthritis and Related Musculoskeletal Diseases	2,000,000	
Title IV, Part I--National Research Service Awards Act	1/	4,344,000 2/

1/ Authorization expires June 30, 1975; extension legislation is proposed.

2/ Funding estimate only.

3/ Total estimated funding for arthritis activities, including those funded under Title IV, Part D.

National Institute of Arthritis, Metabolism, and Digestive Diseases

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	119,203,000	121,203,000	123,203,000	123,203,000
1967	129,908,000	133,687,000	135,687,000	135,687,000
1968	143,954,000	143,954,000	147,204,000	143,954,000
1969	151,718,000	141,287,000	147,287,000	143,888,000
1970	137,668,000	137,668,000	155,000,000	146,619,000
1971	132,152,000	138,339,000	140,339,000	138,339,000
1972	135,594,000	148,365,000	163,790,000	153,164,000
1973	131,857,000	158,307,000	172,991,000	158,307,000 1/
1974	133,718,000	156,004,000	163,110,000	153,671,000 2/
1975	152,896,000	162,142,000 3/	177,935,000	172,980,000
1976	148,409,000			

NOTES:

1/ This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes amount for contracts not considered by the House due to lacking authorization.

National Institute of Arthritis, Metabolism, and Digestive Diseases

Actual

Year	Bureau of the Budget allowance	House allowance	Senate allowance	Appropriation
1966	119,203,000	121,203,000	123,203,000	123,203,000
1967	129,908,000	133,687,000	135,687,000	135,687,000
1968	143,954,000	143,954,000	147,204,000	143,954,000
1969	146,489,000	141,287,000	147,287,000	143,888,000
1970	137,668,000	137,668,000	155,000,000	146,619,000
1971	132,152,000	138,339,000	140,339,000	137,986,000
1972	135,433,000	148,204,000	163,629,000	153,337,000
1973	159,089,000	167,316,000	182,000,000	167,316,000 1/
1974	133,608,000	155,894,000	163,000,000	153,561,000 2/
1975	152,961,000	162,207,000 3/	178,000,000	173,121,000
1976	148,409,000			

NOTES:

1/ This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes amount for contracts not considered by House due to lacking authorization.

Justification

National Institute of Arthritis, Metabolism, and Digestive Diseases

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	566	$12,585,000	556	$12,663,000	-10	+$78,000
Other expenses.....	---	160,395,000	---	135,746,000	---	-24,649,000
Total.....	566	172,980,000	556	148,409,000	-10	-24,571,000

General Statement

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) conducts, fosters, and assists research and training directed toward preventing, diagnosing, treating and controlling the numerous diseases and disorders within its purview. Research and training projects are supported in over 400 non-Federal institutions through the use of grants and contracts, the vast majority of which are awarded to universities and medical schools. Approximately 95% of the funds in these program categories are used for grants and 5% are used for contracts. In addition, the Institute conducts intramural research and clinical research projects at facilities at the National Institutes of Health in Bethesda, Maryland and at field stations in Phoenix, Arizona.

Research grant applications, initiated by the investigator, are reviewed on scientific merit and within the available funds, compete on this basis with other applicants in the same program area. Approximately 676 applicants in 1975 and 312 in 1976 will receive awards from current year funds and will be promised support for an average of two additional years. When these awards are combined with those awards made in prior years which are continuing as a result of a commitment for future support, the Institute will be supporting approximately 1,894 individual research projects in 1975 and estimates it will support a total of 1,420 projects in 1976.

Research and development contracts are also awarded as the result of competition based on scientific merit. Proposals, in this case, however, are solicited in response to specific, well defined objectives developed by the Institute to meet special needs in the development of program objectives.

When the need becomes evident for new development, such as new, more efficient, less costly artificial kidney machines or coordinated clinical evaluation of the efficacy of various regimens in the treatment of regional ileitis, it is usually impractical and inefficient to reassign intramural scientists who have specialized and are engaged in a productive research program. It is likewise seldom that competent outside scientists will volunteer to drop their ongoing studies in

favor of a new problem which has become a special programmatic interest to the Institute. In attempting to meet special needs, direct collaboration is sought with special scientific talent or resources, usually already engaged and competent in closely related efforts and techniques, through the use of research and development contracts.

In addition to universities and medical schools, both non-profit and commercial research organizations may be awarded contracts. In 1975 approximately 91 contracts will be awarded for a one year period, although future support may be planned. In 1976 approximately 83 contracts will be supported.

Previously supported programs supporting research training will be phased out after all current commitments to trainees for fellowships and training grants have been fulfilled. In their place a new program is being initiated to provide for post-doctoral training in specific shortage areas in biomedical and health-related sciences only. The program is directed toward the training of individuals for full-time careers in research and/or teaching. Upon completion of their training, recipients are expected to pursue this objective for a period at least as great as the period of training and individuals who go into clinical medicine or non-health related research may be required to reimburse the Government for the cost of the training.

Under this new program, the Institute expects to make 216 awards in 1975 and 269 in 1976.

The mission of the intramural research area of the Institute is to obtain information and knowledge for the understanding of the fundamental biological processes underlying the major diseases within the Institute's purview. Over 260 research projects including various combinations of laboratory, clinical, epidemiological and biometric investigations are conducted in facilities in Bethesda, Maryland and Phoenix, Arizona. Medical, biological, physical and chemical investigations range from studies of fundamental mechanisms, to specific disease oriented laboratory research, to clinical evaluation and treatment programs. Close collaboration with scientists of other NIH Institutes, other government agencies and outside investigators ensure a minimum of duplication and a maximum exchange of research findings.

DHEW - National Institutes of Health

CROSSWALK - 1975 COLUMN 1976 PRESIDENT'S BUDGET

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
(Amounts in thousands)

Program	Research Grants				Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials							
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Arthritis, Bone and Skin Diseases.....	$14,253	$7,470	---	$518	$2,199	$669		$800		$25,909
2. Diabetes, Endocrinology and Metabolism....	29,608	16,053	$1,516	1,814	2,516	1,191		1,291		53,989
3. Digestive Diseases and Nutrition.....	14,335	11,725	1,300	739	1,659	544		448		30,750
4. Kidney Diseases.....	10,556	3,735	---	139	1,454	506		4,670		21,060
5. Hematology.....	6,149	2,952	---	375	1,260	476		196		11,408
6. Intramural Laboratory and Clinical Research.....							$23,998			23,998
7. Research Management and Program Services... ..									$5,866	5,866
Total Obligations..	74,901	41,935	2,816	3,585	9,088	3,386	23,998	7,405	5,866	172,980

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1976 PRESIDENT'S BUDGET

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
(Amounts in thousands)

Program	Research Grants				Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials							
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Arthritis, Bone and Skin Diseases.....	$15,968	$3,986	---	$290	$45	$1,028		$70		$21,387
2. Diabetes, Endocrinology and Metabolism....	32,073	7,146	1,590	1,531	40	1,233		720		44,333
3. Digestive Diseases and Nutrition.....	16,228	3,952	1,272	641	60	616		1,810		24,579
4. Kidney Diseases.....	10,170	2,565	---	50	60	616		4,000		17,461
5. Hematology.....	7,113	1,560	---	273	30	616		150		9,742
6. Intramural Laboratory and Clinical Research.....							$24,760			24,760
7. Research Management and Program Services.....									$6,147	6,147
Total Obligations..	81,552	19,209	2,862	2,785	235	4,109	24,760	6,750	6,147	148,409

National Institute of Arthritis, Metabolism, and Digestive Diseases

Budget Mechanism

	1975 *			1976		
	Number	FTE 1/	Amount	Number	FTE 1/	Amount
Grants						
Regular						
Non-competing...	1,218		$74,901,000	1,108		$81,552,000
Competing.....	406		24,441,000	188		10,805,000
New.....	270		16,294,000	124		7,204,000
Supplemental....	(98)	---	1,200,000	(98)	---	1,200,000
Subtotal.....	1,894	---	116,836,000	1,420	---	100,761,000
Special						
Multi-disciplinary centers.....			2,816,000			2,862,000
Research career programs.....		130	3,240,000		83	2,440,000
Scientific evaluation....			345,000			345,000
Subtotal.....	---	130	6,401,000	---	83	5,647,000
Total Grants.....	1,894	130	123,237,000	1,420	83	106,408,000
Fellowships						
Non-competing.....		76	1,143,000		202	3,151,000
Competing.....			---			---
New.....		140	2,243,000		67	958,000
Supplemental.....			---			---
Subtotal.....	---	216	3,386,000	---	269	4,109,000
Training Grants						
Non-competing.....		378	9,088,000		26	235,000
Competing.....			---			---
New.....			---			---
Supplemental.....			---			---
Subtotal.....	---	378	9,088,000	---	26	235,000
Laboratory and Clinical Research.			22,713,000			23,462,000
Research & Development Contracts.....			7,405,000			6,750,000
Biometry, Epidemiology & Field Studies.....			1,285,000			1,298,000
Research Management & Program Services.....			5,866,000			6,147,000
Total.....			172,980,000			148,409,000

* Excludes 1973 appropriation restorations.

1/ Full-time equivalents.

Arthritis, Bone and Skin Diseases

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....	---	$25,909,000	---	$21,387,000	---	-$4,522,000
Subactivities:						
Arthritis.....	---	14,084,000	---	11,663,000	---	-2,421,000
Bone Diseases.....	---	7,655,000	---	6,508,000	---	-1,147,000
Skin Diseases.....	---	4,170,000	---	3,216,000	---	-954,000
Total.....	---	25,909,000	---	21,387,000	---	-4,522,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	232	14,253,000	217	16,071,000	-15	+1,818,000
Competing.....	121	7,470,000	65	3,883,000	-56	-3,587,000
Subtotal.....	353	21,723,000	282	19,954,000	-71	-1,769,000
Special.....	---	518,000	---	290,000	---	-228,000
Subtotal.....	353	22,241,000	282	20,244,000	-71	-1,997,000
Fellowships 1/.....	44	669,000	68	1,028,000	+24	+359,000
Training Grants 1/...	93	2,199,000	6	45,000	-87	-2,154,000
Research & Development Contracts.....	5	800,000	1	70,000	-4	-730,000
Total.....	---	25,909,000	---	21,387,000	---	-4,522,000

1/ Numbers are full-time equivalents.

Arthritis & Related Disorders

Arthritis is the term used to describe a group of diseases resulting in inflammation of joints and impairment of their function. The most important of these diseases are rheumatoid arthritis and osteoarthritis. Other diseases in the group include gouty arthritis and the various arthritides of infectious origin.

Altered immune reaction in rheumatoid arthritis: The etiology of rheumatoid arthritis, the most serious and crippling type, is as yet unknown. The hypothesis that it is a disorder of immunity is now widely accepted.

There is much evidence that rheumatoid arthritis may be due to a pathological local immune response maintained by local antigen-antibody complexes. It is considered possible that infection, with viruses or similar organisms, or some other cause may alter a person's immunity so that he becomes sensitive

to proteins produced naturally within his own body, setting up the pattern of inflammation and destruction characteristic of the disease. As immune mechanisms can be moderated and at least partially controlled through immunosuppressive drugs, and infections controlled through chemical agents or vaccines, control or prevention of certain forms of arthritis may eventually be developed along these lines.

Recent studies have indicated that the chronic inflammation observed in tissues of patients with a disseminated form of rheumatoid arthritis is accompanied by increased immune reactions (with enhanced immunoglobulin levels and rheumatoid factor levels in the blood) and by a drop in serum complement values. Numerous studies in recent years have pointed to the involvement of complement, a protein component of blood, in the body's immunological responses, and to low levels of complement in the synovial fluid of some rheumatoid arthritis patients. In the patients studied, complement values were lowest during exacerbations of the joint disease or development of extra-articular complications. The concurrence of low levels of complement with the exacerbations suggests that complement-fixing immune complexes are actively involved in those events. In a related development, a continuing grant-supported study showed this past year that synovial fluid complement determination is of value in the diagnosis and classification of rheumatoid arthritis, particularly in the absence of rheumatoid factor in the blood.

The predominant hypothesis to be pursued in future research on rheumatoid arthritis is that it may be due to a pathological local immune response maintained by local antigen-antibody complexes. Initial sensitization is likely to be caused by an initial infectious process. Attention will be directed to alterations of immune mechanisms through immunosuppressive drugs and to control of infection through drugs or vaccines.

Osteoarthritis-artificial joints: There is no specific therapy for the treatment of osteoarthritis, another major form of arthritis. The most severe cases may require reconstructive surgery to correct deformed joints, or total replacement of nonfunctioning joints with artificial prostheses, as is being done with increasing success in the case of hip joints and knees.

Institute grantees will continue to assemble data from extensive trials of total hip replacement, employing both new and conventional materials. Ceramic materials are being compared with stainless steel, and various types of bone cements are being evaluated; these studies eventually should point to optimal procedures in hip replacement and should aid in other arthritis-related surgery, as for instance knee-joint replacement.

Other arthritis activities: Past Institute studies have contributed significantly to control of the painful symptoms and dangerous complications of gout, but the main research objectives in this disease will continue to be the precise elucidation of the underlying mechanisms of the disorder so as to provide a means of early prevention or effective "cure."

Although the prime responsibility for acupuncture has been delegated to another Institute at the NIH, the NIAMDD is deeply interested in pursuing grant-supported investigations of

acupuncture in the treatment of arthritis. The Institute will also be actively involved in a joint US-USSR program of collaboration with Soviet rheumatologists in arthritis research.

National Arthritis Act

The Institute's programs in arthritis have received additional impetus through the passage of the National Arthritis Act of 1974 (PL 93-640) which calls for a long-range plan of attack on arthritis and related musculoskeletal diseases primarily in the areas of research, development of techniques of community level treatment and public education and professional training.

The first step in implementation of this act will be the creation of a National Commission on Arthritis and Related Musculoskeletal Disorders. This national commission will survey Federal, State, and local health programs and activities relating to arthritis and assess the adequacy, technical soundness, and coordination of such programs and activities, and develop a long-range plan to combat arthritis with specific recommendations for the utilization and organization of national resources for that purpose and will advise the Secretary, the Director of the National Institutes of Health, and the Director of the National Institute of Arthritis, Metabolism, and Digestive Diseases, concerning this plan. This plan will be based on a comprehensive survey investigating the magnitude of arthritis and related musculoskeletal diseases, the epidemiology, etiology, prevention and control including investigation into the social, environmental, behavioral, nutritional, basic biological, and genetic factors, and an evaluation of available scientific information and national resources capable of dealing with the situation. The plan will include a comprehensive program for the National Institute of Arthritis, Metabolism, and Digestive Diseases as well as plans for Federal, State and local programs, including a plan for coordinated research encompassing programs of the various NIH Institutes with research related directly or indirectly to arthritis.

Bone Diseases (Orthopedics)

Orthopedics is that area of medicine and surgery concerned with the musculoskeletal system. Research in orthopedics supported by the Institute is primarily concerned with disorders of the skeletal system in adults, including all types of injuries to bones, joints, muscles, and associated structures, as well as spinal disorders, infections, tumors, and neuromuscular and metabolic diseases of bones and joints. An important objective of the Institute's program in orthopedics is to develop means to prevent complications of arthritic or rheumatic diseases that interfere with joint motion and to develop effective means for relief of these conditions should they occur.

In addition to the above mentioned interest in hip and knee joint replacement, Institute support will be employed in a multi-clinic survey of the long-term effects of surgical removal of rheumatoid arthritis-impaired joint linings (synovectomy) interfering with joint motion. Until recently, synovectomy was generally used only in advanced cases, but surgeons have demonstrated that synovectomy at an early stage may, in some cases, lead to regrowth, in the same joint, of healthy tissue.

Further research is needed to determine which patients are likely to benefit from synovectomy and its long-term effects on the progression of rheumatoid arthritis.

Osteoporosis is a bone disorder affecting middle-aged and elderly persons, particularly women, which causes a gradual decrease in the amount and strength of bone tissue and leads to many of the fractures in the aged. Institute research is centered upon the importance of nutrition and of physical and endocrine factors in the causation, treatment and prevention of this bone disease. Studies on the effect of various levels of mineral intake and on factors that may interfere with the normal absorption of dietary calcium in the digestive system are receiving special emphasis.

Skin Diseases (Dermatology)

Dermatologic disorders currently subject to Institute-supported research include such disease entities as psoriasis, atopic dermatitis, vitiligo, pemphigus, and discoid lupus erythematosus.

At present, grantee scientists are engaged in identifying certain cellular malfunctions with specific chemical disturbances in an attempt to gain a better understanding of the etiology and pathogenesis of the various skin diseases. Disorders of the skin are very widespread conditions that can be highly disabling and incapacitating both physically and psychologically. The annual economic burden of skin disease exceeds $1.5 billion.

One of the most important diseases under investigation is psoriasis, a disfiguring disease that afflicts to a varying degree some 2 to 8 million Americans. One recent survey pointed out that the annual cost of medical care for 4 million "moderate" psoriatics may total $960 million.

The present state of knowledge in psoriasis may serve as an illustra- tion of the problems currently faced in dermatologic research or practice. The basic etiologic mechanism still remains unknown, but recently, Institute- financed epidemiologic studies have shown conclusively that psoriasis is a dominantly inherited disorder. Institute grantees have also provided evidence that disordered metabolism of nucleic acids plays an important role.

In an attempt to accelerate the pace of psoriasis research, the Institute has organized workshops bringing together scientists from different disciplines who have pooled their present knowledge and agreed on future research directions. As a result, a collaborative program in clinical trials of novel topical (surface) agents (developed originally as anti-cancer drugs) for topical treatment of psoriasis is being undertaken.

Photochemotherapy

This next fiscal year, grant-supported investigators will be evaluating the effectiveness and safety of a promising treatment which involves the interaction of light and specific drugs (photochemotherapy). Recently these investigators have reported complete remission of psoriatic skin lesions in a number of patients following oral administration of methoxsalen and exposure to a new form of long-wavelength ultraviolet light.

The Institute's plans embody an effort to expand the existing base of fundamental knowledge relevant to dermatologic research and to extend clinical studies in this field. In addition to basic studies, scientists will investigate further the use of the potent cytotoxic drug methotrexate, effective in treating severe psoriasis, to learn more about its possible side effects, which may include liver damage, depending on the dosage schedule used.

Diabetes, Endocrinology and Metabolism

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate *		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....	---	$53,989,000	---	$44,333,000	---	-$9,656,000
Subactivities:						
Diabetes.....	---	13,322,000	---	10,865,000	---	-2,457,000
Endocrinology.....	---	18,502,000	---	14,299,000	---	-4,203,000
Metabolism.....	---	22,165,000	---	19,169,000	---	-2,996,000
Total.....	---	53,989,000	---	44,333,000	---	-9,656,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	481	29,608,000	436	32,172,000	-45	+2,564,000
Competing.....	258	16,053,000	116	7,047,000	-142	-9,006,000
Subtotal	739	45,661,000	552	39,219,000	-187	-6,442,000
Special.....	---	3,330,000	---	3,121,000	---	-209,000
Subtotal.....	739	48,991,000	552	42,340,000	-187	-6,651,000
Fellowships 1/.....	76	1,191,000	81	1,233,000	+5	+42,000
Training Grants 1/...	105	2,516,000	6	40,000	-99	-2,476,000
Research & Development Contracts.....	10	1,291,000	9	720,000	-1	-571,000
Total.....	---	53,989,000	---	44,333,000	---	-9,656,000

* Excludes 1973 appropriation restorations.

1/ Numbers are full-time equivalents.

Diabetes

Diabetes mellitus is a complex disorder for which there is no known cure. The most obvious defect in diabetes is the body's inability to utilize carbohydrates normally for energy in body functions and growth.

Diabetes can be divided into two clinical types with different prognoses, somewhat different treatment, and related causal mechanisms which, however, lead to dissimilar clinical syndromes. These two types of diabetes are juvenile diabetes and maturity-onset diabetes.

Juvenile diabetes begins during childhood or during the first few decades of life. The disorder progresses rapidly, and most of these patients will eventually develop ketoacidosis with a fatal outcome unless insulin injections are administered

regularly. Even with daily insulin therapy, the life expectancy of the juvenile diabetic is greatly shortened, and he is subject to very serious long term complications, such as premature hardening of the arteries, kidney damage, blindness and neurologic impairment.

Maturity-onset diabetes, which usually has its clinical start after the age of 40, is generally less severe than that seen in young patients and usually does not progress to ketoacidosis with coma, and daily insulin injections are not required for most of those patients. Accelerated hardening of the arteries does occur in maturity-onset diabetes and results in a decreased life expectancy and, depending on the age of onset of the disease and its severity, the same grave complications of juvenile diabetes may gradually make their appearance.

In the United States at present, there are 4 million known patients with diabetes and an estimated 5-1/2 million who are potential diabetics--persons who will develop the disease sometime during their lives. Although diabetes is only rated seventh among causes of death, the true toll is considerably higher, since its vascular complications contribute significantly to cardiac and cerebrovascular mortality.

Artificial Pancreas

In the new fiscal year, investigators will seek new approaches to the problem of transplanting insulin-producing cells with greater potential for survival in recipient experimental animals.

Support will also be provided for the development, expected to be very difficult, of an "artificial pancreas" which would be capable of delivering insulin automatically to the insulin-dependent diabetic patient at the moment he needs it and in the exact dose required.

A primary goal in Institute diabetes research is to understand the basic impairment of insulin activity, a complete knowledge of which would uncover some of the riddles now surrounding the disease. Studies will center on the physiology of insulin, and will seek to establish how this hormone exerts its influence on cell membranes and, consequently, cell metabolism. In the clinical area, Institute grantees will study patients using assays of plasma insulin and measurements of basement membrane thickness in various tissues. The ongoing evaluation of the efficacy and safety of the oral anti-diabetic drugs will continue.

These programs will be greatly enhanced through recent grants to establish five Diabetes-Endocrinology Centers where multidisciplinary research efforts will be made to gain and clinically apply new scientific information. Additional impetus has been given to the Institute's ongoing diabetes program through the passage of the National Diabetes Mellitus Research and Education Act of 1974 (Public Law 93-354) which calls for a long-range plan of attack on diabetes, primarily in the areas of research, development of new techniques of community level treatment and public education, and professional training. The first step in the implementation of this new act, namely creation of a National Commission on Diabetes, has already taken place. During the coming fiscal year this Commission will

develop a long-range plan to combat diabetes mellitus with specific recommendations for the utilization and organization of national resources for that purpose and shall advise the Secretary, the Director of the National Institutes of Health and the Director of the National Institute of Arthritis, Metabolism, and Digestive Diseases concerning this plan. This plan will be based on a comprehensive survey investigating the magnitude of diabetes mellitus, its epidemiology, and its economic and social consequences and on an evaluation of available scientific information and the national resources capable of dealing with the problem. The plan will include a plan for a coordinated research program encompassing programs of the various NIH Institutes which support research related directly or indirectly to diabetes.

Endocrinology and Endocrine Disorders

Endocrinology is concerned with the study of the endocrine glands and their secretions, the hormones, and with the effect of these secretions on the metabolism and physiology of man, especially in regulation of growth, and energy metabolism and responses to stress.

Several Institutes of NIH maintain active programs in the field of endocrinology as it pertains to their specific areas of responsibility. NIAMDD supports the bulk of basic endocrinology research. In addition, studies concern a host of diseases including hypo- and hyperthyroidisms, hypo- and hyperparathyroidisms, osteoporosis, rickets, osteomalacia, growth retardation, and diseases of the pituitary and adrenal glands.

A variety of diseases are associated with derangements of the endocrine system. For example, osteoporosis affecting 30 percent of women over age 50 is thought to be due to a combination of factors chiefly hormonal and nutritional in nature. Hypopituitary dwarfism, a specific type of growth retardation, affects 10,000 American children.

A signal acceleration has taken place during the past 15 years in successful efforts to discover new hormones which regulate important body functions and to elucidate their physiologic and metabolic roles. Much has been learned about the control of their secretion, about their respective target organs, tissues, cells, and intracellular organelles, and about interrelationships of the various hormones and their effect on carbohydrate, fat, and protein metabolism.

Probably one of the most important advances in the field of endocrinology is elucidation by grantee-scientists during recent years of the mechanisms which serve as the bridge and controlling pathway between man's nervous system and his endocrine system. A series of compounds has been isolated, identified and synthesized, which are produced in the hypothalamus portion of the brain. These are carried to the pituitary gland to stimulate or inhibit the release of hormones which affect important body functions, from day-to-day metabolism to reproduction. Studies of these new hypothalamic hormones must be pursued vigorously since their potential for control or correction of a variety of body functions is great.

Further studies will be mounted to characterize somatostatin, the hypothalamic "inhibiting factor" which this

past year was shown capable of markedly inhibiting endogenous physiologic growth hormone release during sleep in normal and acromegalic subjects. Somatostatin may ultimately be of value in the treatment of acromegaly. In preliminary experiments it has also displayed intriguing effects on the hormonal insulin: glucagon balance in diabetes which must be investigated farther since they may unfold new approaches to understanding, and hopefully treating, this disease.

Hormone Developmental Research Program

In recent years, gradually increasing knowledge has revealed the intricate regulatory relationship between hormones and enzymes in most biochemical processes. Alteration of this relationship undoubtedly underlies the functional derangement in many diseases of the blood, bone, liver and intestinal tract. There are numerous examples of areas in protein hormone research which, if stimulated and strengthened by direct, concerted efforts, would yield valuable results directly applicable to diagnosis and patient care in addition to filling gaps in fundamental and clinical endocrine research. At present, pending future expansion, the Institute's hormone developmental research program is comprised of four contracts.

National Pituitary Agency

The Institute has contracted for the operation of the National Pituitary Agency (NPA) at the University of Maryland School of Medicine, Baltimore to increase and improve the collection of human pituitary glands and to provide for the distribution of purified human growth hormone (HGH) derived from them to qualified research scientists. Choice of distribution is made by a well-qualified advisory board of outside consultants. The NPA contract provides for the collection of human pituitary glands, fractionation of their major hormones, and distribution of HGH and other pure fractions to selected investigators for research purposes. At present, HGH can be administered to patients only in conjunction with clinical research studies because it is impossible to collect enough human pituitary glands to obtain sufficient HGH for treatment for all of the children suffering from hypopituitary dwarfism in the United States.

Other Efforts

Another contract provides access for American investigators to the Steroid Reference Collection of the British Medical Research Council. This unique collection, which includes hundreds of reference samples of steroids of highest purity, is the only resource of this kind in the world. Investigators in the United States, including grantees of the Institute, require access to such materials to facilitate and expedite their research since there is no counterpart in the United States to many of these standards.

Another project in this program provides for the collection of rat pituitary glands on a large scale and for their extraction and fractionation to yield purified standardized pituitary hormones: growth hormone, lactogenic hormone, follicle stimulating hormone, and and luteinizing hormone. As in the case of the National Pituitary Agency these purified hormones are made available to qualified, interested investigators with the aid of a specially constituted group of

outside scientific consultants. This project which has been strongly endorsed by investigators in endocrinology provides a much needed source of purified rat pituitary hormones for bioassays and chemical and laboratory studies which have been held up for lack of the purified hormone fractions.

The fourth contract in this program is aimed at providing, in reasonably large quantities, the biologically active metabolite of conventional vitamin D, "1,25 DHCC" (a product of the conversion of vitamin D by the liver and kidneys), to a large number of investigators who are waiting to use it in crucial experiments on calcium and bone metabolism. The substance has only recently been isolated and identified and is not yet available through any other source. Preliminary experiments have emphasized its therapeutic potential in the treatment of otherwise refractory "vitamin D-resistant rickets", and of the serious bone disease which tends to accompany long-standing kidney failure.

Metabolism and Metabolic Diseases other than Diabetes

The Institute supports basic and clinical research on all the complex chemical changes which take place in body tissues on the cellular level, which represent the biochemical basis for all life processes from minute-to-minute energy conversion through growth and aging. This research includes studies of enzymes and their substrates, intermediary metabolites, and minerals, with particular emphasis on regulation of metabolism in normal and disease states. The Institute serves as the focus of research support related to specific metabolic diseases of genetic origin such as cystic fibrosis, Wilson's disease, galactosemia, the various glycogen storage diseases, congenital nonhemolytic jaundice, and many others. Studies will be supported which give promise to facilitate earlier recognition of these "inborn errors of metabolism," inasmuch as early detection and improved medical management can delay the onset of complications and, in some instances, permit a longer survival.

Cystic fibrosis is perhaps the most common ultimately lethal genetic disease of the white population. It is estimated that it afflicts one out of every 1,000-2,000 infants born in the United States each year, that only 50 percent of the victims live past the age of 10, and that 80 percent die before their twenty-first birthday. For clinicians and research scientists alike, cystic fibrosis is a multifaceted disease that offers puzzling fragments yet to be interrelated in a single theory concerning its causation. It is characterized by malfunctioning exocrine glands, which deliver abnormal secretions to the respiratory tract, gastrointestinal tract, and skin.

In the case of cystic fibrosis in particular, research presents difficult problems because the basic biochemical defect is not yet fully understood, and several organ systems are involved. Promising areas of research, especially the identification of the basic biochemical lesion and the development of new methods for diagnosis, treatment, and control, are being pursued. Since the genetic character of cystic fibrosis makes the disorder especially pernicious, an important goal of the program is to develop a reliable, simple method of identifying carriers of the inherited trait so that families at risk can be identified and provided genetic counseling.

Enzyme Replacement

One of the most attractive therapeutic approaches for diseases due to hereditary deficiency of a specific, known enzyme is induction or replacement of such enzyme activity as has been shown possible in the treatment of Fabry's disease. There is also opportunity for progress in dealing with the diseases of genetic origin through a systematic study of deranged metabolic processes. It is estimated that between 50 and 100 different inherited metabolic defects, most of them unknown at this time, will be elucidated if such studies are undertaken on a larger scale. There is need for further investigation of the basic chemistry and function of DNA and RNA, the complex nucleic acids that occupy central roles in the transmission of genetic information from cell to cell and generation to generation. This and other approaches will lead to the assembly of basic general knowledge required to solve the problems of hereditary metabolic disease. With the aid of such additional knowledge, it might eventually be possible to modify the genetic constitution of individuals with selected diseases of this type. Immediate plans involve efforts to extend fundamental studies of genetic material proper, including studies of chromosome structure in man, and of genetic control of protein and enzyme synthesis and regulation.

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Digestive Diseases and Nutrition

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate *		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....	---	$30,750,000	---	$24,579,000	---	-$6,171,000
Subactivities:						
Digestive Diseases...	---	21,797,000	---	16,947,000	---	-4,850,000
Nutrition.....	---	8,953,000	---	7,632,000	---	-1,321,000
Total.....	---	30,750,000	---	24,579,000	---	-6,171,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	233	14,335,000	220	16,050,000	-13	+1,715,000
Competing.....	189	11,725,000	64	4,130,000	-125	-7,595,000
Subtotal.....	422	26,060,000	284	20,180,000	-138	-5,880,000
Special.....	---	2,039,000	---	1,913,000	---	-126,000
Subtotal.....	422	28,099,000	284	22,093,000	-138	-6,006,000
Fellowships 1/.....	35	544,000	40	616,000	+5	+72,000
Training Grants 1/...	69	1,659,000	6	60,000	-63	-1,599,000
Research & Development Contracts.....	3	448,000	5	1,810,000	+2	+1,362,000
Total.....	---	30,750,000	---	24,579,000	---	-6,171,000

* Excludes 1973 appropriation restorations.

1/ Numbers are full-time equivalents.

Digestive Diseases

Digestive diseases are among the most common illnesses in this country, ranking second only to diseases of the heart and circulation in the number of physician office visits or house calls. Cirrhosis of the liver, for example, is the fifth most common cause of death in male adults in America. Peptic ulcer or peptic ulcer symptoms will strike about 10 percent of all American adults at some time in their lives. Many ulcerative colitis patients are afflicted for years with their disorder and must undergo extensive and repeated surgery. While diseases of the stomach and intestines may occur at any age, they most often affect the middle-aged groups. Thus they may cause prolonged and expensive hospitalization and countless social and emotional problems during their victims' most vigorous and productive periods.

Peptic Ulcer

In peptic ulcer research, the laboratory synthesis of gastrin has provided an important research tool for this disease, where excessive secretion of gastric acid underlies the disease process. In rats, the experimental induction of immune antibodies against gastrin can inhibit its potent gastric acid stimulatory action. Recently, novel types of antihistaminic drugs have been found which counteract gastric secretion. One of these is metiamide. Grant-supported investigators have shown that food stimulated acid secretion in duodenal ulcer patients is markedly inhibited by an oral dose of metiamide. Such therapy, if it is without adverse side effects, shows promise of not only healing duodenal ulcers but of preventing their recurrence. Even though there have been reports of possible side effects after the use of this particular new antihistamine, the seriousness of the peptic ulcer problem makes it incumbent that other related drugs be synthesized and investigated in future studies during FY 1976.

As part of the Institute's plan to intensify program efforts in the area of digestive disease, a collaborative research project, the National Cooperative Crohn's Disease Study, will be continued. This study is designed to determine the efficacy of several commonly used regimens in the treatment of regional ileitis (an inflammatory disease of the bowel also known as Crohn's disease), which causes prolonged periods of hospitalization and frequently leads to abdominal operations involving repeated removal of portions of the intestine.

The study, initially involving eight university medical centers, is a controlled, randomized clinical evaluation of three currently used drugs, prednisone, Azulfidine and azathioprine, to determine the effectiveness of these agents. The study examines each drug's effectiveness in preventing intensification and recurrence of the disease.

Gallstone Dissolution

Investigations into the possibility of dissolving gallstones to alleviate the need for recourse to surgery will also continue to be supported. Although medical scientists have been looking for methods to dissolve gallstones for many years, there have been no indications until recently that any medical treatment of gallstones might serve as an alternative to the surgery ultimately performed on one-half of the 800,000 new cases of symptomatic cholelithiasis (galltones) which develop each year. Institute-funded research has shown that long-term administration of a naturally occurring bile acid, chenodeoxycholic acid, can lead to dissolution of cholesterol gallstones (which comprise 90 percent of the gallstones found in patients in the United States). The ability to dissolve cholesterol gallstones, or to prevent their development, would go far toward solving a large public health problem in the United States where about 10% of the population are found to have gallstones upon postmortem examination. Even though not all persons who develop gallstones will suffer the symptoms of the disorder or will be subject to the excruciating discomfort of an acute gallbladder attack, the ability to treat the disease by medical means would avoid many of the 300,000 cases of gallbladder surgery which occur each year. There are 6,000 fatalities each year resulting from this gallbladder surgery.

Based on preliminary encouraging results of this research, plans have been formulated for clinical trials to determine the safety and efficacy of chenodeoxycholic acid treatment in dissolving cholesterol gallstones. This past year, grant-supported investigators have shown that after chenodeoxycholic acid administration was stopped, bile from patients studied reverted to its pre-treatment composition (which is characterized by a high concentration of cholesterol and relatively low bile salt content) and new gallstones developed in several patients.

Digestive Disease Centers

During the next fiscal year, the Institute will make plans to support a number of Digestive Diseases and Nutrition Centers. Initially, the Digestive Diseases and Nutrition Programs of the NIAMDD will accept proposals for Centers devoted to investigations of obesity, peptic ulcer, hepatitis and cirrhosis. The scientific community will be informed when support is available for Centers involved with other areas of research. The objectives of the Centers are to establish environments to develop new, multidisciplinary research approaches to digestive and nutritional diseases, as well as to find ways to improve diagnosis, treatment, and prevention of these disorders.

Nutrition

Improved methods of determining nutritional status and revised norms (daily requirements of specific nutrients), as well as better understanding and diagnosis of malnutrition, are commanding attention in most countries and particularly in developing nations. These advances in knowledge, stemming largely from Institute-supported studies, are forming the basis for more exacting nutrition surveys to pinpoint malnutrition in vulnerable population groups in the United States. Such knowledge will also be invaluable in aiding many developing countries to deal with the widespread malnutrition predicted for the near future if the runaway disproportion between population increase and agricultural self-sufficiency is not drastically reversed.

The nutrition research grants program of the Institute may be divided into two major groupings: normal nutrition and nutritional disorders. Projects related to normal nutrition involve body composition, digestion and absorption of nutrients in the gastrointestinal tract; appetite regulation and food intake; the biochemistry and physiologic role of nutrients and their fate in the body; quantitative requirements of proteins, amino acids, carbohydrates, fats, fatty acids, minerals, trace elements, vitamins, and fluids and electrolytes; interrelations between different nutrients, nutrients and hormones, and nutrients and enzymes; and the relationship of the intestinal flora to nutrition.

Research in abnormal nutrition involves obesity, malabsorption of specific nutrients, discovery and definition of deficiency states, be they primary or secondary to other concomitant disease processes. Another major subdivision relates to nutrition in specific diseases such as diabetes, bone and joint disease, liver disease, infectious disease, inborn errors of metabolism, celiac disease and sprue, skin disorders,

kidney disease and specific stress states (including pregnancy, surgery, trauma, wound healing, and environmental extremes). Parenteral nutrition (administration of nutrients intravenously) is becoming increasingly important in the management of chronic diarrheas of malnourished infants and in a great variety of gastrointestinal dysfunctions and postsurgical states. The real basis for these newer approaches in hyperalimentation rests upon much fundamental research on man's nutritive requirements over many years--research supported in large part by the Institute.

This past year, grantees have demonstrated that pharmacologic doses of vitamin C can destroy substantial amounts of vitamin B12 contained in food. This finding lengthens the list of possible adverse effects of large doses of vitamin C, the currently touted remedy for the prevention and treatment of the common cold. The report concludes that daily ingestion of 0.5 gm or more of vitamin C without regular evaluation of vitamin B12 status is unwise and may result in B12-deficiency anemia.

Vitamin D

Other recent studies have demonstrated that the liver and subsequently the kidney are the sites of conversion of vitamin D into the metabolically active form of the vitamin, essential for intestinal calcium transport and bone mineral mobilization. Subsequent research fully confirmed these findings and demonstrated an indirect role of the kidney in regulation of plasma calcium through a typical "feed-back" mechanism. Chemical characterization of this active form of vitamin D is in progress, and its laboratory synthesis is being actively pursued. Its effectiveness in the treatment of renal osteodystrophy, vitamin D-resistant rickets, and related abnormalities of calcium metabolism will continue to be studied in Fiscal Year 1976.

Obesity

In the meantime, research to facilitate prevention and control of obesity will continue to be supported by the Institute. Overweight and obesity to a degree that interferes with optimal health and longevity affects more than 20 per cent of adults in the United States, and constitutes a public health problem of major concern to the lay public and physicians. Attention will be given to: morphogenesis of adipose tissue cells, multiple aspects of lipid metabolism, effects of periodicity of eating on obesity, effects of neural and other factors on appetite, and the possible role of endocrine dysfunctions and hereditary factors in obesity.

Kidney Disease

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....	---	$21,060,000	---	$17,461,000	---	-$3,599,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	172	10,556,000	138	10,380,000	-34	-176,000
Competing.....	60	3,735,000	42	2,355,000	-18	-1,380,000
Subtotal.....	232	14,291,000	180	12,735,000	-52	-1,556,000
Special.....	---	139,000	---	50,000	---	-89,000
Subtotal.....	232	14,430,000	180	12,785,000	-52	-1,645,000
Fellowships 1/.....	32	506,000	40	616,000	+8	+110,000
Training Grants 1/...	63	1,454,000	6	60,000	-57	-1,394,000
Research & Development Contracts.....	68	4,670,000	64	4,000,000	-4	-670,000
Total.....	---	21,060,000	---	17,461,000	---	-3,599,000

1/ Numbers are full-time equivalents.

Nephrology in its broadest sense is defined as the study of the kidney and related organs in health and disease. The primary functions of the kidney include elimination of nitrogenous and other waste products as well as regulation of the body's water balance, and that of salts and minerals in the blood and tissues. In addition, the kidney is implicated in the regulation of blood pressure and in other hormonal activities, including stimulation of red blood cell formation.

Diseases of the kidney may be classified as follows: (1) hypersensitivity diseases, in which kidney tissue is destroyed by an immune reaction initiated by several causes, including hypersensitization during a previous streptococcal infection; (2) infections, in which kidney tissue is attacked and destroyed by microorganisms; (3) circulatory diseases and hypertension, in which the kidney is affected as a result the constant, abnormally high blood pressure and of disease of the blood vessels; (4) metabolic diseases, in which the kidney is secondarily affected, as in diabetes or gout; (5) developmental disorders in which the kidneys fail to develop in a normal fashion; and (6) obstructive conditions, in which urine flow is blocked, resulting in pressure damage to the kidney and repeated infections.

It is estimated that on a national basis the death rate from primary or secondary kidney disease is 29 per 100,000 population. The 60,000 annual deaths due to kidney failure are

exceeded only by deaths due to heart disease, cancer, cerebral vascular accidents and traumatic accidents. Eight million individuals suffer from disorders of the kidney or urinary tract.

Bright's Disease

Glomerulonephritis (Bright's disease) is a serious renal disorder characterized by an inflammatory reaction in the kidney glomerulus, causing leakage of blood and blood constituents into the urine, and by deterioration of the filtering function of the kidney. Several studies during the next fiscal year will evaluate the efficacy of immunosuppressive and other drugs in the treatment of glomerulonephritis and other chronic immunologic glomerular diseases.

Drug for Nephrosis

Nephrosis (idiopathic nephrosis) is a disorder of kidney tubules which leads to a characteristic and constant loss of protein into the urine, resulting in low levels of protein in the blood and generalized fluid retention and tissue swelling (edema). The drug azathioprine (an immunosuppressive agent) has been tried in corticosteroid-drug-resistant patients with encouraging results. The investigators conclude that azathioprine merits further trials in patients with the nephrotic syndrome, especially preadolescents with growth retardation secondary to corticosteroid therapy, or in other patients for whom steroid treatment is contraindicated. Studies will be carried out on many other aspects of kidney disease in an effort to improve early diagnosis of renal disorders and to find more effective methods of slowing down the rate of renal impairment in kidney disorders currently not amenable to outright prevention or cure. The role of basic studies in renal disease is of utmost importance since, as yet too little is known to permit us to attack the root causes of the most serious renal disorders.

Artificial Kidney Program

Although artificial kidneys have been known for over two decades, and have been used in cases of poisoning or acute kidney failure, repeated use of these devices in any one patient was limited. Institute-supported development of permanently implanted, connected plastic tubes in an artery and vein of the forearm, providing an indwelling shunt, has started a new era of hemodialysis in patients with permanently impaired kidney function. Repeated use of artificial kidneys in such patients on a thrice weekly schedule now permits the saving of lives that would otherwise be lost because of inevitable fatal uremia.

As the life-extending potential of artificial kidneys became apparent nine years ago, the Institute's special Artificial Kidney-Chronic Uremia Program was created to expedite research and development in this field.

Consultants advise that fundamental research on the nature of uremia must proceed side-by-side with efforts to improve dialysis apparatus and techniques. Thus, studies on the metabolic characteristics of kidney failure and on its largely unknown toxic products are fundamental to rational design of a more effective dialysis machine or device, and for the initiation of a productive program of applied research and

development for still simpler, more economical, and more efficient dialysis treatment.

The high hospital overhead, the limited functional life of apparatus, and the need for costly professional personnel are primarily responsible for the current high cost of dialysis, which averages $32,000 per patient per year in hospitals. Home dialysis, in contrast, costs from $3,500 to $7,000 per year after the initial outlay for training and equipment.

Medicare Provision

An important event two years ago was the revision of the Social Security law to provide financial assistance to patients with irreversible kidney failure. This Medicare provision provides payment of dialysis treatment or kidney transplantation to all end-stage kidney disease patients covered by Social Security, or their dependents. It is expected that this will result in a population of patients on maintenance dialysis numbering 40,000-50,000 within the next few years.

The cost of this program is estimated to rise to about $700-800 million annually or more. Any improvement in current dialysis therapy which can be developed by the Artificial Kidney-Chronic Uremia Program which would enhance the medical rehabilitation of the patients or would make the currently costly and lengthy treatment briefer and more effective, will bring about significant human benefits in terms of well-being and ability to work full-time, and will result in substantial savings of Federal funds.

Development projects

At present about 70 research and development projects are supported by research contracts with universities, nonprofit and industrial research laboratories to provide a broad approach to problems of highest priority. Projects are focused on critical problem areas such as clinical trials of more efficient or less costly dialyzers, development of special adsorbents for uremic toxins, studies to elucidate the nature of the aberrant metabolic changes in uremia, and the maintenance of a national registry of all patients who are being maintained with the aid of dialysis. The program is also funding studies aimed at isolation and identification of toxic factors which must be removed from the patient's blood, in addition to metabolic wastes and other substances known to accumulate during kidney failure. A large number of research projects is also devoted to the pathophysiology of uremia in an effort to prevent or control long-term clinical complications in patients who have lost their kidney function and are being maintained with the aid of artificial kidneys.

Today about 15,000 patients with permanent kidney failure are being maintained with the aid of dialysis. More than 4,000 of these patients dialyze themselves at home, at great savings in cost. An entirely new generation of simpler, less expensive artificial kidney machines has been developed under Institute funding and sponsorship. The trend toward home dialysis, facilitated by these developments, avoids most of the prohibitive expense associated with hospital dialysis and has made it possible for about 1,500 new patients since last year to obtain relatively inexpensive life-saving chronic dialysis treatments.

Ultrafiltration Cell

Accomplishments this past year include those of contract-supported scientists who have designed an ultrafiltration cell to remove excess sodium and water efficiently, rapidly, and inexpensively from fluid-overloaded patients on chronic hemodialysis. The device can be used as a separate unit or in series with an artificial kidney. The cell may also enable physicians to treat more rapidly and efficiently patients suffering from non-renal disorders whose edema is secondary to cardiac failure and those with acute pulmonary edema who previously required emergency hemodialysis or prolonged treatment with diuretics and sodium and fluid restriction. Although used to date only in a dialysis setting, it is suggested that such therapy could logically be extended to patients with refractory chronic edematous states (such as chronic congestive heart failure) or with pulmonary edema, and would conceivably replace costly and prolonged hospitalization with one or two relatively brief ultrafiltration treatments.

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Hematology

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....	---	$11,408,000	---	$9,742,000	---	-$1,666,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	100	6,149,000	97	6,879,000	-3	+730,000
Competing.....	48	2,952,000	25	1,794,000	-23	-1,158,000
Subtotal.....	148	9,101,000	122	8,673,000	-26	-428,000
Special.....	---	375,000	---	273,000	---	-102,000
Subtotal.....	148	9,476,000	122	8,946,000	-26	-530,000
Fellowships 1/.....	29	476,000	40	616,000	+11	+140,000
Training Grants 1/...	48	1,260,000	2	30,000	-46	-1,230,000
Research & Development Contracts.....	5	196,000	4	150,000	-1	-46,000
Total.....	---	11,408,000	---	9,742,000	---	-1,666,000

1/ Numbers are full-time equivalents.

Research on blood disorders and anemias supported by the Institute includes that on defective hemoglobin synthesis (genetically transmitted abnormalities of the hemoglobin molecule) such as Cooley's anemia; hemolytic anemias, of both hereditary and acquired origins; anemias associated with chronic diseases and nutritional deficiencies; and autoimmune blood diseases such as thrombocytopenic purpura.

Cooley's Anemia

New initiatives and research are forthcoming in the area of Cooley's anemia following passage of the National Cooley's Anemia Control Act. This Act provides for expanded programs of research, diagnosis, prevention and treatment of the disorder, an inherited blood disease which occurs primarily in persons of Mediterranean ancestry. In the United States most of the victims are of Italian, Greek, Turkish, Southern French or North African descent, although the disease is not limited to these groups. Worldwide, the thalassemias, of which Cooley's anemia is a predominant example, represent the most common inherited single gene defect.

As in many genetic blood disorders, those who inherit the trait for the disease from only one parent will become "carriers" and are usually free of severe symptoms; those who inherit the gene from both parents have the overt disease. This severe form of the disease can be expected to occur in one fourth of the children of parents who both carry the trait.

Cooley's anemia is characterized by the production of abnormally thin red blood cells with abnormal mechanical fragility giving rise to a profound anemia which appears soon after birth. Severe effects of the disease in addition to the anemia include an enlarged spleen and a grossly overactive bone marrow which may produce thickening of facial bones.

The development of an effective iron chelating agent is one of the two areas of highest feasibility and priority in the area of Cooley's anemia; the other matter given top priority is a simple and reliable screening test for the trait. The urgency for developing a better iron chelating agent is based on the fact that the final illness and death of patients with Cooley's anemia is due primarily to the deposit of large quantities of iron in vital organs (heart, liver and kidneys); this iron has its origin from the numerous blood transfusions which must be given to patients with Cooley's anemia to keep them functioning.

Diagnostic techniques in the various blood diseases have become highly developed, and accurate diagnosis is frequently the key to successful treatment. Institute-supported research has contributed much to current knowledge of the molecular structure of hemoglobin and of the disordered amino acid sequence in abnormal hemoglobins.

One of the most important stimuli in hematology research is the continuing need for defining the metabolic mechanisms responsible for anemia. Hemoglobinopathies, mineral, vitamin, hormone and enzyme deficiencies, hemolysis due to pathologic immune mechanisms, and drug sensitivity--the major etiologic entities involved in anemias--will all be under intensive investigation in Fiscal Year 1976.

Abnormal hemoglobin variants of animals and man will be studied and the exact structure and composition of their molecules will be defined. Drawing on this basic biochemical background, studies will continue on the structural-functional relationships of abnormal hemoglobins producing such human diseases as Cooley's anemia and other hereditary hemoglobinopathies.

Intramural Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	460	$10,547,000	450	$10,528,000	-10	-$19,000
Other expenses.....	---	13,451,000	---	14,232,000	---	+781,000
Total.....	460	23,998,000	450	24,760,000	-10	+762,000

Introduction

The mission of the intramural research area of the Institute is to obtain information and knowledge for the understanding of the fundamental biological processes underlying the major diseases within the Institute's purview. Over 260 research projects including various combinations of laboratory, clinical, epidemiological and biometric investigations are conducted in facilities in Bethesda, Maryland and, to a lesser extent, in Phoenix, Arizona. The range of studies can best be described by the names of the laboratories, which are as follows: Nutrition and Endocrinology, Biochemistry and Metabolism, Chemistry, Experimental Pathology, Chemical Biology, Biochemical Pharmacology, Physical Biology, Biophysical Chemistry, Chemical Physics, and Molecular Biology. The branches for clinical investigations are titled Arthritis and Rheumatism, Metabolic Diseases, Digestive and Hereditary Diseases, Clinical Endocrinology, Pediatric Metabolism, and Clinical Hematology.

Close collaboration with scientists of other NIH Institutes, other government agencies and outside investigators ensures a minimum of duplication and a maximum exchange of research findings.

Arthritis and Related Disorders

Intramural investigators share the belief of their colleagues in laboratory and clinics around the country, that rheumatoid arthritis is the result of chronic inflammation, probably triggered by an abnormal immune reaction. Although the mechanisms of damage remain unproven and obscure, they are endeavoring to discover whether the degenerative process results from an infection, an autoimmune reaction (mistaken attack by body defense systems on its own tissue), or quite plausibly, a combination of these two factors.

Arthritis Treatment

In the treatment of rheumatoid arthritis, this coming year intramural investigators will continue to scrutinize closely an anti-cancer agent, cyclophosphamide. Although preliminary

results have been promising, scientists are anxious to learn more about the mechanism of action of the drug in ameliorating rheumatoid arthritis or in slowing its progression and they will continue to investigate its potent side effects, which may place limitations on its more widespread use.

The relatively gradual destruction of cartilage, bone, and periarticular supporting structures, which is characteristic of rheumatoid arthritis and is its most disabling feature, is ascribed to invasion of the structures by chronic inflammatory granulation tissue. There is some reason to believe that timely surgical removal of this tissue will prevent progressive destruction, and thus research will include experimental synovectomies to ascertain their worth.

SLE Research

One of the major connective tissue diseases for which the Institute seeks a means of control, cure, or prevention is systemic lupus erythematosus (SLE). This condition is manifested by various disorders in the structure and activity of the skin, joints, blood vessels, and internal organs. It is an insidious, inflammatory disease with a progressive course and eventual fatal outcome in many patients. Although the cause of SLE is not known, much evidence points, as in the case of rheumatoid arthritis, to a dysfunction of the body's immune system, which may or may not be tied to a previous infectious process or drug toxicity.

Although the mechanisms of SLE are not understood, the disease can appear as a result of hypersensitivity to certain drugs, and this phenomenon is among those being studied at the NIH Clinical Center. Patients also are under investigation there in a therapeutic study involving the immunosuppressive drug cyclophosphamide in the treatment of the kidney complications of SLE.

National Arthritis Act of 1974

The recently enacted National Arthritis Act of 1974 (PL 93-640) also provides for the initiation of basic and clinical orthopedic research to be conducted within the framework of the Institute's intramural research program. The Act directs that from the appropriation for this Institute not less than $500,000 per year be obligated for this program. Means for supporting these activities are currently being reviewed.

Diabetes and Other Metabolic Diseases

Intramural scientists are engaged in studies on the basic impairment of insulin activity in diabetes. Investigations during the forthcoming year will center on the physiology of insulin, and how this hormone exerts its influence on cell membranes and cellular metabolism. Institute scientists will study ways in which insulin acts upon individual body cells primarily by binding to specific receptor sites on cell membranes.

Scientists will also examine how the multiple effects of insulin, e.g., increased glucose transport into the cell, decreased mobilization of fat, increased glycogen synthesis, depend upon one or more "second messengers" that act within the cell, such as spermine and spermidine (which have been found to mimic intracellularly some of the actions of insulin) or "cyclic AMP." Continuance of such fundamental studies is essential for elucidation of the mechanisms by which insulin exerts its multifarious effects on cellular processes, and may permit development of rational and effective treatments for diabetic patients.

The normal cell activities including normal carbohydrate metabolism which take place within cells and which require the presence of insulin are known to be initiated and supported by the presence of insulin molecules in close contact with the outer aspect of the cell membrane.

This past year, intramural investigators reported that in obesity the cell membranes of fat cells appear to be refractory to the effects of insulin and have found that insulin binds to the membranes of target cells only half as well in fat persons as in nonobese persons. This decreased binding is due to a deficiency in the number of insulin "receptor spots" on the membranes of target cells. Thus, obese persons require higher levels of insulin than do thin people to achieve the same effects on glucose metabolism. When fat people fast, and individual fat cells shrink consequently, the insulin receptor sites on their target membranes revert to their normal number.

Institute researchers will also continue clinical studies of cystic fibrosis (CF), with additional basic studies in such disciplines as biochemistry, genetics, and molecular biology. Efforts will be geared toward uncovering the specific basic biochemical aberrations of this disease in expectation that in this way, improved detection, control and therapy will be possible. For example, since the components of external secretions play such important roles in the pathogenesis of cystic fibrosis, intensive studies will be conducted to isolate the abnormal factors in such exocrine gland secretions as saliva.

Cystic Fibrosis

Much of the therapeutic effort in cystic fibrosis is directed toward chronic lung disease, the severity of which usually determines the CF patient's fate. Although aerosols, mist tents, mucolytic agents and postural drainage are used with some success in removing mucus from the lungs, an advance in the treatment of CF would be the development of an effective pharmacologic means of increasing airway clearance. This past year, Institute scientists have demonstrated that the outward-bound tracheal mucus velocity is markedly decreased in CF patients because the normal sweeping action of the tiny hair-like projections ("cilia") which line the lung's major air passages is impaired. Administration of a new beta-adrenergic agent, terbutaline, has been found to increase tracheal mucus velocity significantly and, thus, this pharmacologic agent may be of therapeutic significance in CF.

Endocrinology

One main thrust of Institute endocrinology research is to learn the precise mechanisms by which hormones influence the metabolism and physiology of man. Recent findings are leading to a better understanding of disorders of the parathyroid gland, such as hyperparathyroidism. This disease, marked by an oversecretion of parathyroid hormone, causes decalcification of bone, an abnormally high blood calcium level, and can lead to kidney stones, bone cysts, and other problems.

Studies will be carried out on effects of calcium or EDTA infusions and changes in diet on the secretion of parathyroid hormone. Recent use of selective venous catheterization combined with radioimmunoassay for parathyroid hormone has proved of value also in localizing parathyroid tumors incompletely removed at earlier surgical explorations.

Attention will also be given to renal and gastrointestinal responses to the effects of the hormone. These studies will further be applied to selected patients with hypoparathyroidism, rickets, osteomalacia, vitamin D-resistant rickets, osteoporosis, and certain other abnormalities of bone metabolism.

Parathyroid Hormone

A recent finding indicates that parathyroid function is an important influence on urinary excretion of cyclic 3'5' -AMP and that this nucleotide is involved in the mechanism of action of parathyroid hormone. Clinical investigations based on these findings suggest that a constitutional defect of the hormonally sensitive enzyme adenyl cyclase may be the cause of pseudo-hypoparathyroidism, and further cases of this disorder will be studied.

In other studies, Institute scientists will pursue their preliminary findings regarding the administration of thyroxine. The scientists have shown that weekly (rather than more frequent) administration of thyroxine, a synthetic thyroid hormone, is a safe and effective means of controlling hypothyroidism in young patients without cardiovascular disease.

This past fiscal year an Institute scientist has reported on an important metabolic study of the effects of space flights on the human body. The exhaustive mineral and nitrogen balance studies of the Skylab astronauts have revealed significant in-flight losses of calcium, nitrogen and phosphorus which could impair normal musculoskeletal function in future long-term flights. He concluded that although prolonged space flights of 6 to 9 months might reasonably be predicted as "safe," an 18 to 36 months trip to Mars could have serious effects on bone and muscle unless protective counter measures can be developed.

The weightlessness data obtained also suggest that research on osteoporosis, a bone-thinning disorder associated with aging, should give greater attention to the possibility that increased weight-bearing stress might act as a deterrent to or may possibly even lead to a reversal of this condition which is very prevalent in advanced age, particularly among women.

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Digestive Diseases

The digestive tract is a primary focus of the Institute's clinical research activities. To emphasize further digestive disease research, the NIAMDD reorganized its intramural research activities on digestive disorders into a Digestive Diseases Branch and is now composed of three sections: Gastroenterology, Diseases of the Liver, and Phoenix Clinical Research Section. The new Branch supersedes the former Digestive and Hereditary Diseases Branch, and will continue to conduct clinical and laboratory investigations to determine abnormalities in structure and function of the esophagus, stomach, small and large intestines, pancreas and liver, and will conduct research on certain hereditary metabolic diseases. Work will be directed at an understanding of human disease and its treatment in terms of underlying derangements in the body's metabolism and physiology.

The cost of the 300,000 cholecystectomies (gallbladder removals) performed annually in the U.S. approaches one billion dollars and includes 6,000 fatalities. Fifteen million people in this country alone are estimated to have gallstones with about three times the incidence in females compared with males. As previously described in the extramural section on digestive diseases, an exciting new concept of treating cholesterol gallstones medically rather than surgically has shown considerable promise. The oral administration of a natural bile acid, chenodeoxycholic acid, has resulted in the diminution or disappearance of cholesterol gallstones in most of the subjects tested in a grant-supported study at the Mayo Clinic. During this coming year the Digestive Diseases Branch will participate in therapeutic trials of this medical approach to the dissolution of gallstones.

G.I. Tract Lavage

During the next fiscal year a clinical study will deal with the use of lavage of the entire GI tract, by means of saline solutions ingested voluntarily, as a means of preparing patients for barium enema and other X-ray studies, and for proctoscopy, colonoscopy, or other endoscopic procedures. Drinking saline may prove to be more acceptable to patients than the traditional procedures using castor oil, or other purgatives, followed by multiple enemas, and may have a less irritant effect on the colonic mucosa, thus improving accuracy of the diagnostic studies. If this proves to be the case, both applicability and accuracy of these tests in the study of any disease affecting the colon may be improved.

Gallbladder Disease

Reports from the Institute's Southwestern Field Studies Section had previously revealed that the Pima Indians of Arizona have a rate of gallbladder disease that is six times higher than that found in a similar study of Caucasians in Framingham, Mass. It has also been found that among the Pima Indians, gallbladder disease is extraordinarily frequent in both males and females, and that less than one half of the affected subjects had displayed clinical symptoms.

The establishment of the patho-physiologic basis of cholesterol gallstone formation in the American Indian and other

populations as the result of secretion of bile which is abnormally low in bile salt content has led to the realization that the prevention and dissolution of gallstones by oral administration of bile salts may be possible. The suitability of the Pima Indian population for the demonstration of the potential of this mode of therapy has led to the design of a large, nation-wide clinical trial, funded by the Institute, to determine the ability of chenodeoxycholic acid to dissolve asymptomatic gallstones.

Hematology

Hematology represents an important part of the Institute's research mission. Among Institute research goals is a definition of the specific defects in various blood disorders, as well as knowledge of the precise steps in normal and abnormal blood clotting mechanisms, with application of resulting findings to improved diagnosis and therapy.

During the coming fiscal year, Institute clinical research in blood disease will stress, among other studies, the biochemistry of blood coagulation with particular reference to the development of better forms of therapy for various congenital and acquired hemorrhagic diseases. Such disorders as hemophilia A or B, von Willebrand's disease, hemophiloid conditions such as Factor V or Factor VII deficiency, circulating anticoagulants, afibrinogenemia, and fibrinolysis, as well as obscure, undiagnosed bleeding disorders, will be studied. New approaches to therapy of acute and chronic idiopathic thrombocytopenic purpura, in which the number of blood platelets is severely reduced leading to the danger of uncontrollable hemorrhage, and reduced platelet levels in systemic lupus erythematous will also be evaluated.

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Research Management and Program Services

Authorizing Legislation: Public Health Service Act Title IV Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	106	$2,038,000	106	$2,135,000	---	+$97,000
Other expenses.....	---	3,828,000	---	4,012,000	---	+184,000
Total.....	106	5,866,000	106	6,147,000	---	+281,000

Within this activity, general direction, coordination and administration of the resources of the total Institute are provided by the Institute Director, his immediate staff and the office of administrative management including contract negotiations and awards. The review and approval of grants functions include review for scientific merit and program relevance and maintenance of surveillance over each grant project. Scientific information functions are also conducted under this activity.

Nearly two-thirds of the resources of this activity are devoted to review and approval of grants functions including professional and supporting personnel who are responsible for the administration of the Institute's several grants activities. They assist in the planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; review and evaluation of research and training grant applications for presentation to the National Advisory Arthritis Council; required Council staff assistance; liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interested organizations; continuous surveillance of scientific activities and progress; and recording and reporting of fiscal and scientific information relevant to all transactions.

The entire increase for this activity in this budget request is required for mandatory items primarily including annualization of the cost of recent pay increases and an increase of this Institute's proportionate share of increased costs of centrally furnished services such as receipt and initial review of all grant applications, maintenance of buildings and grounds, custodial services, communications, and transportation.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Arthritis, Bone and Skin Diseases (Public Health Service Act Title IV Parts D and I)

1975 Estimate			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$25,909,000	Indefinite	---	$21,387,000

Purpose: The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) conducts, fosters and assists research and training directed toward preventing, diagnosing, treating and controlling the numerous diseases encompassed in this activity. Programs are carried out through the use of research grants (approximately 85% of the funding), research and development contracts, fellowships and training grants.

Accomplishments in 1975: In 1975, 353 research grants, 44 fellowships, 31 training grants, and 5 contracts were awarded which represent increases of 13 research grants, 1 fellowship and 4 contracts and a decrease of 21 training grants from the 1974 levels. Of the research grants awarded, 232 were noncompeting continuations of previous awards and 121 were new and competing continuations. Of the fellowships awarded, 19 were noncompeting continuations of previous awards and 25 were new awards. All of the 31 training grants were noncompeting continuations.

Objectives for 1976: The estimate for 1976 provides for 282 research grants, 68 fellowships, 2 training grants and one research and development contract. Of the research grants, 217 will be noncompeting continuations and 65 will be new or competing renewal awards. All of the 68 fellowships will be for noncompeting continuations. Both training awards will be noncompeting continuations.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Diabetes, Endocrinology and Metabolism (Public Health Service Act Title IV Parts D and I)

1975 Estimate			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$53,989,000	Indefinite	---	$44,333,000

Purpose: The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) conducts, fosters and assists research and training directed toward preventing, diagnosing, treating and controlling the numerous diseases encompassed in this activity. Programs are carried out through the use of research grants (approximately 85% of the funding), research and development contracts, fellowships and training grants.

Accomplishments in 1975: In 1975, 739 research grants, 76 fellowships, 35 training grants, and 10 contracts were awarded which represent increases of 5 research grants and 4 contracts and decreases of 47 fellowships and 26 training grants from the 1974 levels. Of the research grants awarded, 481 were noncompeting continuations of previous awards and 258 were new and competing continuations. Of the fellowships awarded, 28 were noncompeting continuations of previous awards and 48 were new awards. All of the 35 training grants were noncompeting continuations.

Objectives for 1976: The estimate for 1976 provides for 552 research grants, 81 fellowships, 2 training grants and 9 research and development contracts. Of the research grants, 436 will be noncompeting continuations and 116 will be new or competing renewal awards. All of the 81 fellowships will be for noncompeting continuations. Both training awards will be noncompeting continuations.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Digestive Diseases and Nutrition (Public Health Service Act Title IV Parts D and I)

1975 Estimate			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$30,750,000	Indefinite	---	$24,579,000

Purpose: The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) conducts, fosters and assists research and training directed toward preventing, diagnosing, treating and controlling the numerous diseases encompassed in this activity. Programs are carried out through the use of research grants (approximately 85% of the funding), research and development contracts, fellowships and training grants.

Accomplishments in 1975: In 1975, 422 research grants, 35 fellowships, 23 training grants, and 3 contracts were awarded which represent an increase of 17 research grants and decreases of 9 fellowships, 8 training grants and 2 contracts over 1974. Of the research grants awarded, 233 were noncompeting continuations of previous awards and 189 were new and competing continuations. Of the fellowships awarded, 9 were noncompeting continuations of previous awards and 26 were new awards. All of the 23 training grants were noncompeting continuations.

Objectives for 1976: The estimate for 1976 provides for 284 research grants, 40 fellowships, 2 training grants and 5 research and development contracts. Of the research grants, 220 will be noncompeting continuations and 64 will be new or competing renewal awards. All of the 40 fellowships will be for noncompeting continuations. Both training awards will be noncompeting continuations.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Kidney Disease (Public Health Service Act Title IV Parts D and I)

1975 Estimate			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$21,060,000	Indefinite	---	$17,461,000

Purpose: The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) conducts, fosters and assists research and training directed toward preventing, diagnosing, treating and controlling the numerous diseases encompassed in this activity. Programs are carried out through the use of research grants (approximately 85% of the funding), research and development contracts, fellowships and training grants.

Accomplishments in 1975: In 1975, 232 research grants, 32 fellowships, 21 training grants, and 68 contracts were awarded which represent increases of 37 research grants, 3 fellowships and 9 contracts and a decrease of 8 training grants from the 1974 levels. Of the research grants awarded, 172 were noncompeting continuations of previous awards and 60 were new and competing continuations. Of the fellowships awarded, 14 were noncompeting continuations of previous awards and 18 were new awards. All of the 21 training grants were noncompeting continuations.

Objectives for 1976: The estimate for 1976 provides for 180 research grants, 40 fellowships, 2 training grants and 64 research and development contracts. Of the research grants, 138 will be noncompeting continuations and 42 will be new or competing renewal awards. All of the 40 fellowships will be for noncompeting continuations. Both training awards will be noncompeting continuations.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Hematology (Public Health Service Act Title IV Parts D and I)

1975 Estimate			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$11,408,000	Indefinite	---	$9,742,000

Purpose: The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) conducts, fosters and assists research and training directed toward preventing, diagnosing, treating and controlling the numerous diseases encompassed in this activity. Programs are carried out through the use of research grants (approximately 85% of the funding), research and development contracts, fellowships and training grants.

Accomplishments in 1975: In 1975, 148 research grants, 29 fellowships, 16 training grants, and 5 contracts were awarded which represent decreases of 10 research grants and 6 training grants and increases of 5 fellowships and 5 contracts over the 1974 levels. Of the research grants awarded, 100 were noncompeting continuations of previous awards and 48 were new and competing continuations. Of the fellowships awarded, 6 were noncompeting continuations of previous awards and 23 were new awards. All of the 16 training grants were noncompeting continuations.

Objectives for 1976: The estimate for 1976 provides for 122 research grants, 40 fellowships, one training grant and 4 research and development contracts. Of the research grants, 97 will be noncompeting continuations and 25 will be new or competing renewal awards. All of the 40 fellowships will be for noncompeting continuations. The training award will be a noncompeting continuation.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Intramural Laboratory and Clinical Research (Public Health Service Act Title IV Parts D and I)

1975 Estimate			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
460	$23,998,000	Indefinite	450	$24,760,000

Purpose: The mission of the intramural research area of the Institute is to obtain information and knowledge for the understanding of the fundamental biological processes underlying the major diseases within the Institute's purview. Over 260 research projects including various combinations of laboratory, clinical, epidemiological and biometric investigations are conducted in facilities in Bethesda, Maryland and Phoenix, Arizona. Medical, biological, physical and chemical investigations range from studies of fundamental mechanisms, to specific disease oriented laboratory research, to clinical evaluation and treatment programs. Close collaboration with scientists of other NIH institutes, other government agencies and outside investigators ensure a minimum of duplication and a maximum exchange of research findings.

Objectives for 1976: The entire increase for this activity in this budget is required for mandatory items primarily including annualization of the cost of recent pay increases and an increase of this Institute's proportionate share of increased costs of centrally furnished services such as patient care, computer services, maintenance of buildings and grounds, custodial services, communications, and transportation.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Research Management and Program Services (Public Health Service Act Title IV Parts D and I)

1975 Estimate			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
106	$5,866,000	Indefinite	106	$6,147,000

Purpose: This activity provides the overall scientific and administrative management of the Institute. Functions include analysis evaluation, planning and direction of the various research and training programs; review, approval and administration of grants and contracts; collection and dissemination of scientific information; and administrative management of the operating areas of the Institute.

Objectives for 1976: The entire increase for this activity in this budget request is required for mandatory items primarily including annualization of the cost of recent pay increases and an increase of this Institute's proportionate share of increased costs of centrally furnished services such as receipt and initial review of all grant applications, maintenance of buildings and grounds, custodial services, communications, and transportation.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$148,409,000	$37,102,000
Total, obligations	148,409,000	37,102,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Arthritis, Bone and Skin Diseases	---	$21,387,000	---	$4,840,000
Diabetes, Endocrinology and Metabolism	---	44,333,000	---	11,468,000
Digestive Diseases and Nutrition	---	24,579,000	---	5,797,000
Kidney Diseases	---	17,461,000	---	4,267,000
Hematology	---	9,742,000	---	3,004,000
Intramural Laboratory and Clinical Research	450	24,760,000	450	6,190,000
Research Management and Program Services	106	6,147,000	106	1,536,000
Total obligations	556	148,409,000	556	37,102,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	556	556
Full-time equivalent of all other positions	57	57
Average number of all employees	621	621
Personnel compensation:		
Permanent positions	$10,776,000	$2,694,000
Positions other than permanent	570,000	142,000
Other personnel compensation	62,000	15,000
Subtotal, personnel compensation	11,408,000	2,851,000
Personnel benefits	1,255,000	576,000
Travel and transportation of persons	280,000	70,000
Transportation of things	75,000	5,000
Rent, communications and utilities	370,000	92,000
Printing and reproduction	270,000	67,000
Other services	4,608,000	913,000
Payment to NIH Management Fund	9,901,000	2,477,000
Project contracts	6,750,000	750,000
Supplies and materials	1,890,000	475,000
Equipment	850,000	200,000
Grants, subsidies and contributions	110,752,000	28,626,000
Total obligations by object	148,409,000	37,102,000

National Institute of Arthritis, Metabolism, and Digestive Diseases

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the National Institute of Arthritis, Metabolism, and Digestive Diseases consistent with the 1976 Estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

MONDAY, *April 14, 1975.*

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

WITNESSES

DR. DONALD B. TOWER, DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DR. ELDON L. EAGLES, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
ECKART WIPF, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
ROBERT L. SITHENS, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We will continue with the National Institutes of Health. We now have the National Institute of Neurological and Communicative Disorders and Stroke. The presentation will be made by Dr. Donald B. Tower, the Director. We have a biographical sketch of you, Doctor, which we will place in the record at this point.

[The biographical sketch follows:]

BIOGRAPHICAL SKETCH OF DONALD BAYLEY TOWER

Position: Director, NINCDS.

Birthplace and date: Orange, N.J., December 11, 1919.

Education: A.B., Harvard College, 1941; M.D., Harvard Medical School, 1944; M. Sc., McGill University, 1948; Ph. D., McGill University, 1951.

Experience: Director, NINCDS, May 31, 1974–present; acting director NINDS, May 1, 1973–May 30, 1974; chief, Laboratory of Neurochemistry, IR, NINDS, May 1961–May 1973; head, section on Amino Acid and Electrolyte Chemistry, LNC, IR, NINDS, May 1961–May 1974; medical director, USPHS (active), 1958–present; acting associate director, EP, NINDB, July 1967–June 1968; Chief, Section on Clinical Neurochemistry, IR, NINDB, July 1953–May 1961; assistant professor of experimental neurology, McGill University, 1952–53; associate neurochemist, Montreal Neurological Institute, 1951–53; externe (neurology), National Hospital, Queen Square, London, 1951 (5 months); research fellow, Montreal Neurological Institute, 1947–51; assistant resident (neurosurgery), Montreal Neurological Institute, 1948–49; medical officer, USNR, 1945–46 (active duty, Philippine theater); interne (surgery), University of Minnesota Hospitals, 1944–45.

Association memberships: American Academy of Neurology; American Association for the Advancement of Science; American Chemical Society; American Neurological Association; American Society for Neurochemistry; American Society of Biological Chemists; Canadian Neurological Society; Canadian Physiological Society; International Brain Research Organization (Member, Central Committee); International Society for Neurochemistry.

Special awards, citations, or publications: Alpha Omega Alpha; Sigma Xi; Markle scholar, 1951–1953; chief editor (western hemisphere), Journal of Neurochemistry, 1968–73; chairman, neurochemistry delegation to U.S.S.R. under United States-Soviet exchange program, 1969; Lennox guest lecturer, American Epilepsy Society, 1970; author of over 90 scientific papers and monographs.

Mr. FLOOD. I see you have some people there with you.

Dr. TOWER. Yes, sir.

I have Dr. Eagles, our Deputy Director on my left, and Mr. Wipf, our executive officer; Mr. Sithens, our budget officer; and you know Dr. Lamont-Havers and Mr. Miller already I presume.

Mr. FLOOD. Yes.

I see you have a prepared statement, Doctor. How do you want to handle that?

Dr. TOWER. I would like to read it if I may, sir.

Mr. FLOOD. All right, suppose you do.

GENERAL STATEMENT

Dr. TOWER. Mr. Chairman and members of the committee, it is again my privilege to discuss with you the current research programs of the National Institute of Neurological and Communicative Disorders and Stroke, NINCDS.

May I call your attention to the fact that we have just changed our name to take account of the fact that we are responsible for communicative disorders, a very large health problem, involving lots of patients, and a major component of our research and training programs.

TWENTY-FIFTH ANNIVERSARY

On August 15, 1975, the Institute will mark the 25th anniversary of the signing of Public Law 692, 81st Congress, establishing the Institute. In retrospect we can point to a quantum increase in our knowledge about the nervous system; to a vital augmentation in the numbers of basic neuroscientists and clinical researchers in the United States; and to the development of a variety of important new investigative, diagnostic, and monitoring techniques and instrumentation, notably in the electronics, radiation, and miniaturization fields. We can also point to the conquest or distinct amelioration of a number of disorders of the nervous system, such as phenylketonuria (PKU), Parkinson's disease, epilepsy, myasthenia gravis, otosclerosis, laryngeal cancer, congenital rubella, Gaucher's disease, and so forth; and to significant discoveries, like the slow virus etiology of presenile dementias, several new chemical transmitters of nerve impulses, key roles for immunological mechanisms in the sclerosing or demyelinating disorders, and many others which promise future solutions to even more disease problems. To celebrate the anniversary, the NINCDS will publish a two-volume compendium of this quarter century of research advances fostered by the grant, training and contract support provided by NINCDS funds.

May I say, sir, that we have just received a birthday present from the World Health Organization which has chosen this Institute as one of seven collaborating centers in the neurosciences around the

world. The other centers are in Marseilles, Strasbourg. both in France, in Nigeria, in Montreal, in Mexico City, and in Moscow.

We look forward to this as an opportunity to spread some of the findings and information which these centers, and particularly ours, have gained to the developing countries of the world.

Clearly there are many disorders and problems still to be elucidated. Strokes and injuries to head and spinal cord rank as the third and fourth leading causes of death in this country, and together they represent the largest group of disabled and crippled adults in America. Altogether, the neurological and communicative disorders afflict more than one-fifth of our population, and because of their chronic, lifetime handicapping nature they impose enormous social and economic burdens, in addition to the immediate problems of health care and rehabilitation.

Hence the NINCDS must continue to support research and research training in its four major program areas, as well as in its intramural laboratories at Bethesda. Approximately 80 percent of our fiscal year 1975 funds are invested extramurally in approximately 1,300 grants and 80 contracts comprising by program areas the following proportions of the total fiscal year 1975 NINCDS budget: 11.8 percent for research in communicative disorders; 44.2 percent for research in neurological disorders; 12.2 percent for research in stroke and central nervous system trauma; and 10.6 percent for research in fundamental neurosciences not readily identifiable with any of the other three program areas. In accordance with these budgetary categories, we are this year substituting for our present extramural grants program and our collaborative and field contract program a reorganizational amalgamation into the four program areas just described. Thus, the emphasis will be on program rather than on the instrument of support. We expect this reorganization to be operational by the beginning of fiscal year 1976.

Let me briefly highlight for you some of the current progress in each of these four program areas.

COMMUNICATIVE DISORDERS

In the communicative disorders, the NINCDS is now funding 33 program project, center and other targeted research grants at a level of nearly $5 million, as well as over 107 regular research grants and 13 contracts.

During fiscal year 1975, the NINCDS sponsored several workshops on the current status and future research needs in such problem areas as secretory, serous, otitis media—a prime cause of childhood deafness—laryngeal papillomatosis—recurring benign tumors of the vocal cords in children—and cochlear or auditory implants—devices that hopefully may restore a measure of hearing to the profoundly deaf. The two workshops on cochlear implants have already generated recommendations for grant or contract supported research projects now being implemented by the NINCDS. Among other major concerns, the problems of noise as it affects hearing and speech will be assessed in several contracts now in the solicitation and negotiation stages, and all such NINCDS projects in the noise area are being co-

ordinated with other Public Health Service groups, notably the National Institute of Environmental Health Sciences and the National Institute of Occupational Safety and Health, as well as the Environmental Protection Agency.

Let me say parenthetically that the two other Institutes in HEW, NIEHS, NIOSH, and we, have set up an informal coordinating committee for this particular purpose so that the various programs and projects can be properly coordinated amongst three groups in DHEW.

NEUROLOGICAL DISORDERS

For the *neurological discorders*, the NINCDS is funding in fiscal year 1975 a total of 54 clinical research centers, program project and other targeted research grants totaling almost $10 million, as well as more than 746 regular research grants and 47 contracts.

There have been key advances in our knowledge of the biofeedback systems which modulate the balance between excitatory and inhibitory circuits in the brain. Such studies are relevant to epilepsy, Parkinson's disease, dystonia, Huntington's disease and other disorders which result from imbalances in such circuitry. A new two-drug combination therapy for Parkinson's disease is about to be released for clinical use, and the next generation of drugs is in active development and testing at our Bethesda Laboratories.

EPILEPSY

Several new drugs for epilepsy (clonazapam and dipropylacetate) should be ready for clinical release next year. The feasibility stage of our comprehensive epilepsy program is nearly completed and proposals are now being sought for the full-scale programs, one or more of which we expect to fund in fiscal year 1975.

SLOW VIRUSES

The pace of virological and immunological research continues to quicken. An important new development is the finding that after experimental inoculation of slow virus agents of the kuru-scrapie group into primate brains, electron microscopic changes in nerve cells can be regularly seen as early as 1 month later, whereas brain wave (EEG) abnormalities only appear after 3 months and the clinical signs are not discernible before 2 years. The recent isolations of latent viruses of the foamy and adeno types from brains have important implications because their presence in brain tissue complicates the use of DNA hybridization techniques, a powerful tool for identifying in tissue samples the presence of pathological viruses, and because they may themselves function as "helper" viruses to facilitate the emergence of a pathogenic slow virus directly or after immunosuppressive therapy.

I would like to acknowledge here in our slow virus program the very extensive cooperation from the National Cancer Institute with regard to our oncoming facility at the Frederick Cancer Research Center. We have a building there which will come on line, hopefully, by the end of the next fiscal year.

The recognition of the role of the thymus gland in the production of T-lymphocytes—one of the key elements in antibody production and development of cellular immunity—sheds new light in the previously suspected connection between the thymus and myasthenia gravis, a serious neuromuscular disorder. The connection may be explicable on the basis of thymus-produced circulating particles which affect neuromuscular junctions to produce the myasthenic syndrome but can be counteracted by prednisone, one of the most effective current therapeutic agents.

MULTIPLE SCLEROSIS

Studies on immunosuppressive therapy, use of transfer factor, evaluation of HLA-antigen profiles, and use of immunoelectron microscopy and viral probes exemplify the surge in research following the workshops and report of the National Multiple Sclerosis Commission last year. Several surveys recommended by the Commission are now in progress, including an epidemiological study of multiple sclerosis in the Orkney and Shetland Islands, where the incidence of multiple sclerosis is the highest in the world. In May, I will accompany a team of U.S. scientists to the U.S.S.R. to confer with their Soviet counterparts on multiple sclerosis in that country. With respect to amyotrophic lateral sclerosis (ALS), a focus with an incidence even higher than that on Guam has been discovered by one of our NINCDS scientists in Western New Guinea. In addition to earlier circumstantial evidence for a viral etiology, viral probing of brain samples from Guamanian ALS patients has turned up a C-type virus particle, the significance of which is under active investigation.

STROKE AND CENTRAL NERVOUS SYSTEM TRAUMA

In stroke and central nervous system trauma, the NINCDS is currently funding 63 program project, clinical research center and other targeted research grants totaling over $10 million, plus more than 59 regular research grants and 16 contracts.

A highlight of fiscal year 1975 has been the work of the NINCDS Advisory Council Subcommittee on regeneration in the central nervous system. Five workshops have been held, with a final report summarizing current status and recommended areas of promising research submitted to the March 1975 meeting of the NINCDS Advisory Council. I was privileged to attend each of these workshops and can assure you that exciting new avenues of research are opening up, such as the glial cell elaboration of nerve growth factor, collateral axonal sprouting from surviving neurons in areas of injury, delineation of cell recognition factors in formation of cell-to-cell connections and mechanisms of elongation of growing nerve tips.

I think it fair to say that the picture for the spinal cord injured, the paraplegic, has brightened considerably.

Progress in the field of stroke is perhaps not spectacular but it continues to be steady. The latest available age-adjusted mortaliy rates indicate that there has been a significant decrease from 88.8 per 100,000 population in 1950 to 68.5 per 100,000 in 1969. In the future, I think

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we may expect even lower figures as a result of more recent advances in diagnostic and therapeutic measures. These include X-ray angiographic and tomographic techniques to visualize cerebral vessels three-dimensionally; radioisotope scintiscanning to localize damaged brain areas; computerized axial tomography (CAT—or EMI—scans), a most effective noninvasive technique for high resolution visualization of density differences in brain tissue caused by edema, hemorrhage, decreased blood supply, etc.; ultrasonic monitoring of cerebral blood flow; microsurgical correction of malformed blood vessels in brains or of narrowed or stenotic carotid (feeder) arteries to brain; surgical linking of superficial temporal (scalp) arteries to the middle cerebral (brain) artery, a procedure designed to bypass blocked feeder vessels and restore blood flow to the brain; and the use as appropriate of anticoagulant drugs (including aspirin), blood pressure lowering regimes, clot dissolving (thrombolytic) agents, and drugs for control of brain edema and of blood vessel spasm. One of our NINCDS scientists has suggested the intriguing possibility of infusing fat (or lipid) degrading enzymes to lower blood levels of specific lipids believed to be involved in promoting the deposition of atheromatous plaques that narrow the calibre of cerebral and cardiac arteries.

FUNDAMENTAL NEUROSCIENCES

Finally, in the fundamental neuroscience program the NINCDS is funding some 159 grants and 5 contracts for research on basic problems that are not readily categorized in the other three program areas. Two of the most exciting areas in the entire fundamental neuroscience field are those concerned with central nervous system regeneration (relevant especially to paraplegia and stroke) and with neuroimmunology (relevant to a host of degenerative disorders of the nervous system including multiple sclerosis, presenile dementias, et cetera). These are truly frontiers where spectacular advances may be expected in the next few years.

Much of the work in our laboratories at Bethesda is in the fundamental neuroscience category. To keep pace, the Institute has established three new laboratories within the past year: one in neuro-otolaryngology (with special emphasis on the mechanisms responsible for the transduction of sound waves by the mechanoreceptors of the inner ear into coded nerve impulses to the higher brain centers); another in neuroimmunology (with a broad emphasis on viral and autoimmune diseases and an extensive interlaboratory collaborative program); and a third in neuropharmacology (with particular expertise in the pharmacological manipulation of central nervous system pathways in disorders where excitatory-inhibitory imbalances exist; I refer to such disorders as parkinsonism).

Our intramural program has been strengthened by the appointments this year of a new Scientific Director, Dr. Thomas Chase, and a new Clinical Director, Dr. Donald Calne.

INFORMATION

In the area of information, the Institute is continuing the preparation and distribution of pamphlets for patients and physicians to pro-

vide them with the salient features and research progress in the various neurological and communicative disorders. We have increased the number and variety of audio and video tapes of lectures by experts on various advances in clinical research for loan or distribution to physician groups and leading institutions. This has been a pioneering approach by the NINCDS Office of Scientific and Health Reports.

I would like to insert here information that was just compiled this past week. We have 28 tapes on neuromuscular disorders for which we have had over 1,200 requests by 39 medical schools, 20 non-Federal hospitals, 14 VA hospitals, 7 military hospitals, 22 medical groups, and 30 physicians.

There is already a long waiting list for these tapes. We now have just prepared 15 video tapes on multiple sclerosis as a result of a recent workshop on progress in that area and there are plans for others in the area of the communicative disorders.

Mr. FLOOD. What do you mean that information just came to you in the last week?

Dr. TOWER. This was just compiled in the last week on the basis of requests over the last few months.

SPINAL MANIPULATIVE THERAPY

During fiscal year 1975, the Institute held a workshop at Bethesda on the fundamental bases of spinal manipulative therapy, at which leaders from the chiropractic, osteopathic, physical medicine, and neuroscience professions discussed together the present knowledge and state-of-the-art with respect to back pain and related clinical problems. A number of areas for further basic and clinical research were identified and will be summarized in a forthcoming report. Another workship is planned to bring together the professional and lay experts concerned with the problem of autistic children, so that the dimensions of the problem, criteria for evaluation, and fruitful directions for research can be identified.

During fiscal year 1975, the NINCDS also brought together at Bethesda representatives from virtually all the professional societies and voluntary health agencies in the fields of neurological and communicative disorders. Over 60 organizations and more than 100 representatives attended. As a result, there was better acquaintance with the NIH and the NINCDS, a realization of the need for greater coordination and cooperation rather than a fragmented or individual approach, and an opportunity for the many organizations to get to know each other. Finally, the NINCDS Office of Scientific and Health Reports has initiated with the PHS Regional Office in Atlanta an experimental project to provide that region with information on various major clinical problems in the neurological and communicative disorders in forms suitable for dissemination to practicing physicians and also to identify NINCDS grantees in the region upon whom the regional office can call for local extensions of this informational effort. This approach should do much to meet the needs for better informing the practicing physician and the public.

In conclusion, Mr. Chairman, the budget request for the National Institute of Neurological and Communicative Disorders and Stroke

for 1976 is $114,955,000. I shall be pleased to answer any questions and supply additional information as desired for the record. Thank you.

Mr. FLOOD. Doctor, your budget for your Institute shows a net reduction of $27,079,000.

Dr. TOWER. Yes, sir.

PROGRAM REDUCTIONS

Mr. FLOOD. You told us about all your programs. Which of your programs is hit the hardest by your proposed reduction?

Dr. TOWER. Well, sir, the programs are all hit. The place where the impact will be felt most is in the noncompeting continuation grants. You understand that our grant program represents approximately 70 percent of our budget.

Mr. FLOOD. As a matter of fact, over 50 percent of this cut was applied to the neurological disorders, wasn't it?

Dr. TOWER. Yes, sir.

Mr. FLOOD. More than 50 percent.

Dr. TOWER. That is our largest program.

Mr. FLOOD. But more than 50 percent of the cut was applied to the neurological program; is that right? The answer is yes, isn't it?

Dr. TOWER. The answer is yes, sir; that represents over 50 percent of our grant program.

Mr. FLOOD. It is still 50 percent of the cut.

Dr. TOWER. Yes, sir.

Mr. FLOYD. Why did you apply such a large portion of the cutback of over 50 percent to that particular program area?

Dr. TOWER. The cuts have been applied in proportion to the size of the programs and since this program represents well over half of our grant money, it is not surprising that the largest cut would be there.

GRANT COMMITMENTS

Mr. FLOOD. You mentioned this just a minute ago.

Can you meet your noncompeting grant commitments in fiscal year 1976 with this budget?

Dr. TOWER. May I preface my answer to that question, sir, with a general concern about the budgetary issues that I have.

Mr. FLOOD. That is all right, but you remember the question.

Dr. TOWER. I will answer your question.

Mr. FLOOD. Tell me can you do it and then, if you want to make a speech, go ahead.

First of all, can you meet the noncompeting grant commitments in fiscal 1976 with this budget?

Dr. TOWER. The answer is "No."

Mr. FLOOD. Go ahead. The curtain is now up.

Dr. TOWER. I will answer it more specifically. We will fall about $4 or $5 million short. However, The Department has taken the position, as you have already been told by both Dr. Cooper and Dr. Lamont-Havers, that we should reduce some of the lower priority noncompeting grants or actually terminate some of them.

That has been the formula developed by the Department. I would like, however, sir, if I may, to insert a concern that I have on the

general issues. There are several problems which have concerned all of us that have——

Mr. FLOOD. What general issue?

Dr. TOWER. The general issue of budget reductions and budget changes over the years.

NEW AWARDS UNDER 1975 LEVEL

Mr. FLOOD. We are not talking about that right at this minute. We are talking about noncompeting grant commitments. Let me ask you this: If we were to restore your budget to the 1975 level, how many new grants would you be able to award then?

Dr. TOWER. I will have to phrase my answer in this way, sir.

If you mean that we should fund——

Mr. FLOOD. I mean exactly what I said. If we restore your budget to the 1975 level, how many new ones could you grant? How many new awards?

Dr. TOWER. If we fund all the commitments, then we will have left over approximately $10 million which will fund approximately 140 new grants, in addition to those already specified in the fiscal year 1976 budget as submitted.

Mr. FLOOD. That is the answer, 140 new grants, period.

SPINAL CORD INJURY

We hear a great deal about the need to organize spinal cord injury care in the country and people tell us that the medical care and rehabilitation services, too, should be coordinated.

What are your views on this subject? What are you doing to reduce the obvious fragmentation that exists now in the system?

Dr. TOWER. We believe strongly in coordination, sir. The centers which we have, acute spinal cord injury clinical research centers, are mostly located in juxtaposition with rehabilitation centers that are operated by the Social and Rehabilitation Services of HEW, in addition to which we have close coordination with a number of the Veterans Administration centers designed for this purpose as well.

Mr. FLOOD. How are you coordinating your efforts in spinal cord injury with the Social and Rehabilitation Services at HEW?

Dr. TOWER. Most of our centers are located where their rehabilitation centers are also located.

Mr. FLOOD. Are you funding any projects together with SRS?

Dr. TOWER. No, sir; we have no joint funding.

Mr. FLOOD. Which are designed now to organize the treatment for the spinal cord injury?

Dr. TOWER. May I add to what I said that when the SRS rehabilitation centers programs are reviewed our staff sits in on the reviews so that the liaison and our efforts can be coordinated in that way.

Mr. FLOOD. Are these spinal cord injury centers becoming an integral part—a lot is being done about this now and there has been a lot of testimony so far—of the Emergency Medical System that we are appropriating funds for under the Health Services Administration?

The reason I brought that up, Doctor, is that, you know, you have an accident; there is very little time for a doctor to restore any neuro-

logical disorders. He might comb your hair or something, but a neurological disorder, and so much has been said so far in the testimony this year and toward the end of last year, the Emergency Medical System; big deal.

Dr. TOWER. Well, these centers are part of the Regional Emergency System in each case. Our centers are concerned with the first 24 to 48 hours. This is where the research effort is being focused. I might say as to some of our other centers, head injury, for example, we just established one down in Galveston which is the center for that part of Texas for all injuries, so that we are into this. I must agree with you that we are not doing as much as we should be, but I think you understand this is very difficult to coordinate at the Federal level, since much of it must be done out there in the regional areas with the center people themselves.

X-RAY SCANNER

Mr. FLOOD. Last year we heard quite a good deal about the development of a new computerized X-ray scanner to be used in diagnosing and monitoring stroke.

What do you have to report on that technique this year?

Dr. TOWER. This has pretty well revolutionized the way of handling many of the acute and even some of the chronic disorders of the nervous system because it allows a good look at the brain, the various changes that go on with blood supply, with increase or decrease of fluid, atrophy, and so on. It not only improves diagnosis, it also pertains to the brain without having to take a look inside or without having to stick needles into the patient.

I think one of the most interesting aspects of this is that the engineers have realized the importance of this and they are continually improving these instruments so that the capabilities today are about 100 percent better with these instruments that they were about 2 years ago and new ones are being brought on the market.

We understand that there is one now which will allow scans of the whole body. So far this capability has been limited to the head. There was an experimental one down at Georgetown which did the whole body but that has not really come to fruition yet.

Now we understand there is one made by the EMI Co., which will allow whole body scans, and we are particularly interested in this for the possibility of looking at the spinal cord because this would improve greatly our ability to manage our spinal cord patients.

Mr. FLOOD. When do you expect this technique to be part of the health care delivery system?

Dr. TOWER. That is a bit difficult to answer because these are very expensive instruments and I don't know that one can anticipate that they will be on every street corner, so to speak. They cost between $300,000 and $500,000 apiece, so that it is quite an expenditure for a small hospital, community hospital. Most of them are still localized in large urban centers.

Mr. FLOOD. What would be the immediate impact if this scanner was to become part of the practicing physician's operation?

Dr. TOWER. If the whole body scanner proves to be as promising as——

Mr. FLOOD. Did you ever hear the term "practicing physician's armamentarium"?

Dr. TOWER. I don't think most practicing physicians would be able to afford it and I don't think this is the appropriate place for it. It is part of the workup in a major hospital center for major medical and neurological problems.

MULTIPLE SCLEROSIS

Mr. FLOOD. Doctor, what recommendations did the National Advisory Committee on Multiple Sclerosis make in fiscal year 1976? That is in terms of research to be pursued and the dollar level to be invested.

Dr. TOWER. The recommendation for this year, and I think we are pretty much in phase on that, was that in 1976 we should expend approximately $5.8 million on additional research specific to multiple sclerosis, and then they made a recommendation for additional basic research which was quite a bit larger than that, $12.5 million.

Mr. FLOOD. What will you be able to do under the 1976 budget?

Dr. TOWER. With the budget as proposed we will not be able to meet the recommendations of the commission.

DIABETIC NERVE DISEASE

Mr. FLOOD. We understand the single most common manifestation of the effects of diabetes is upon the peripheral nervous system, and, of course, sooner or later that is going to be involved significantly in nearly 100 percent of all diabetes patients, I suppose.

What are you doing about diabetic nerve disease?

Dr. TOWER. This is a major problem, as you indicated, particularly in the diabetic who is not well controlled. I might insert parenthetically that we have other problems. Stroke is a very common complication of diabetes and also diabetic retinopathy. Retinopathy is a major problem.

This falls into a large group of disorders in which the nutrition and metabolism to the peripheral nerves is impaired. We understand a great deal about this but not all of it. It requires more research. I think it is characteristic of diabetes that much of the problem of the nerve peripheral system is related to the blood supply to the nerves.

Mr. FLOOD. Last year you told us the effective control of diabetes could also contribute to the control of stroke. You know about the Diabetes Act, Public Law 93-354. The act itself requires each institute to make some budget contribution to diabetic research. How much have you set aside for diabetic research and where will you invest the money, what areas?

Dr. TOWER. We have a considerable amount of money invested in areas which bear upon diabetes. We looked over our grants and contracts portfolio——

Mr. FLOOD. How much would you say? How much in dollars?

Dr. TOWER. That specifically designed for diabetes came to about $500,000. However, a great deal of our fundamental and applied research is directly relevant because one of the problems with the nervous system is its supply of glucose. Diabetes represents a disturb-

ance of the metabolism of glucose, so all the studies which we have which are relevant to blood supply of the brain, to glucose supply to the brain, are applicable to diabetes at the fundamental level. Thus, many millions of dollars actually are going to help forward knowledge in that area.

COMPREHENSIVE EPILEPSY PROGRAM

Mr. FLOOD. Let me ask you, as a matter of fact, about your efforts to implement the comprehensive epilepsy program. Do you care to tell us what has been going on during fiscal year 1975 in just that area?

Dr. TOWER. The 11 feasibility studies which we initiated at the beginning of fiscal 1975 are practically finished now.

Mr. FLOOD. For the record, what is epilepsy? You better have a sentence or two to define it.

Dr. TOWER. Epilepsy is a disorder which is characterized by spontaneous, paroxysmal, repetitive discharges of nerve cells in the brain. It can be caused by a large number of factors, the most important of which is injury to the brain. It is a major problem. It affects 2 million to 4 million people in this country.

The feasibility stage of the comprehensive epilepsy program is over, or almost over. We now have in-house over 20 proposals for the full-scale program. These will be reviewed. Those that rank high in the review will be visited and a decision will be made as to how many will be funded before the end of this fiscal year.

We expect to be able to fund, depending on how many turn out of the review, one, two, or three comprehensive programs during this fiscal year.

HUNTINGTON'S DISEASE

Mr. FLOOD. What research are you doing on Huntington disease and what is Huntington's disease?

Dr. TOWER. Huntington's disease is a hereditary disorder which strikes the patient in middle life, in the fourth and fifth decades of life, so that it is not known which children of Huntington's parents will come down until they are in middle adult life. There is no known way of determining who will have it before the clinical symptoms develop.

It is characterized by degeneration in the brain, with progression to dementia and death. It is a very tragic disorder.

Mr. FLOOD. Hereditary?

Dr. TOWER. Yes.

Mr. FLOOD. On either side, male or female?

Dr. TOWER. Yes.

Mr. FLOOD. Which one?

Dr. TOWER. Both.

Mr. FLOOD. Does the Mendel theory apply at all?

Dr. TOWER. Yes, it does.

Mr. FLOOD. How much money did you spend in 1975 on that?

Dr. TOWER. The specific expenditure on Huntington's disease was very small, approximately $555,000. However, the reason for that is that we have no idea what the cause of Huntington's disease is beyond the fact that it is a hereditary disorder. Therefore, most of the expenditures must be in the fundamental neuroscience area.

Within the past 2 years evidence has accumulated indicating a specific deficit of one of the transmitters of nerve impulses in the central nervous system. This is called gamma-amino butyric acid, or GABA for short.

This is very analogous to the situation in Parkinsonism in which dopamine is deficient and L-dopa therapy has been so effective. It turns out that in the brains of Huntington's patients there is a deficiency of GABA. We hope that this may be the clue that will allow us to attack this problem successfully.

It is too early to tell. I was earlier this year at a conference out in California at which we discussed the whole spectrum of GABA and its functions in the central nervous system and a great deal of attention was devoted to Huntington's disease at that time. This will all be published soon.

AUTISTIC CHILDREN

Mr. FLOOD. Last year we began to be particularly concerned, as you recall, and in our report, that we filed with the 1975 appropriation bill we expressed concern about the relatively little research being done with autistic children.

By the way, what are autistic children?

Dr. TOWER. Autistic children have been classically described as a form of childhood schizophrenia. It turns out that this is an incorrect characterization.

Mr. FLOOD. You better translate that, too.

Dr. TOWER. Schizophrenia is a major mental disorder affecting mostly adults but it does occur in childhood in which there is a lack of insight or appreciation of certain areas of reality on the part of the schizophrenic patient.

It turns out that the autistic child really should not be characterized as childhood schizophrenic. The disorder comes on much earlier and is of a different type. These children tend to be noncommunicative. They may not talk at all. They may be very withdrawn. Some of them may actually indulge in self-mutilation and self-damage.

By careful work by both parents and teachers in some cases this can be minimized and actually a number of the children are eventually rescued.

Mr. FLOOD. Have you expanded your research in this area?

Dr. TOWER. What we have done, sir, is we have met with the people from the National Society for Autistic Children and discussed with them the present situation. They are very knowledgeable and forward-looking people. They have collected together all the work which has now been going on. What we now propose to do is set up a workshop, probably this summer, in which we will bring together all the people who have knowledge about this disorder.

Mr. FLOOD. What do we know so far about the problem now? Is it caused by a physical abnormality?

Dr. TOWER. No, sir; we think it is probably related to an imbalance in the excitatory and inhibitory influence in the central nervous system.

DYSTONIA

Mr. FLOOD. We have received a lot of letters, concerning a disease called dystonia musculorum deformans. What is it?

Dr. TOWER. This falls in the same general category. This is an imbalance in the impulses of the nervous system which produces grotesque movements and is in at least three forms. Two are hereditary, transmitted from parents to child. A third form can be acquired in several ways.

Mr. FLOOD. Directly from parent to child?

Dr. TOWER. In the dominant hereditary form, yes, sir. On the acquired form, we don't know how that is acquired in all cases. It could be caused by a virus or toxic agent of some sort. In many cases we simply don't know. It is clear here that they are disorders of certain enzymes and this is, of course, characteristic of many hereditary disorders. It is hoped that such clues will advance our studies.

Mr. FLOOD. Are you doing any research in this area?

Dr. TOWER. Yes, sir.

Mr. FLOOD. Do you have any statistics as to the number of people afflicted by this?

Dr. TOWER. I don't offhand. I can get it for you.

Mr. FLOOD. Suppose you do.

Dr. TOWER. Yes, sir.

[The information follows:]

The statistics on the number of people afflicted with dystonia, as in many other disease areas, are not firm. The estimates, however, indicate that at least 4,000 persons are afflicted. There are several thousand persons who are afflicted with the acquired variety. With the hereditary form, less than 1,000 have now been identified. However, this is a significant increase over the number identified in 1967, which was less than 40 families. At that time the institute conducted a survey and discovered over 500 families. Since then the institute has maintained a registry of families in the United States with one or more members affected by the hereditary dystonias. As of early 1975, over 700 families have been identified, several with more than 10 members affected.

The risk for dystonia is not spread evenly through the population. Those with Ashkenazic Jewish ancestry are at highest risk for the recessive type. Probably 1 of every 100 in this Jewish group carries this gene. When both parents happen to carry the gene recessive dystonia is produced in about one out of four of their children.

DIAGNOSTIC AND TREATMENT TECHNIQUES

Mr. FLOOD. Can you supply for us a few of the significant diagnostic and treatment techniques that have been developed in your institute, say in the last 3 years, which are now being routinely used by the practicing physician?

Dr. TOWER. Yes, sir.

Let us take epilepsy first. In the institute we have developed the techniques for measuring the blood levels of the anticonvulsant drugs used in epilepsy.

Mr. FLOOD. That is the practicing physician now?

Dr. TOWER. And have disseminated this information to the country so it has now become standard practice to measure the serum blood levels of the anticonvulsant drugs as the prime way of managing the patient.

Mr. FLOOD. That is one. What else?

Dr. TOWER. Second, in parkinsonism much of the development of the new two-drug therapy which will come out shortly has been developed in our institute. This is already in use experimentally and the FDA will shortly approve this for general use.

Mr. FLOOD. Shortly?

Dr. TOWER. Yes, sir.

Mr. FLOOD. This afternoon?

Dr. TOWER. No; it will be this summer we understand.

Mr. FLOOD. What about practicing physicians at 4 o'clock?

Dr. TOWER. A lot of them are using it already.

Mr. FLOOD. In addition to that, in the last 3 years now? You have given us 2.

Dr. TOWER. In myasthenia gravis which is a muscular disorder, the prednisone high alternate-day dosage has been established as the treatment for myasthenia gravis in our laboratories. This is now the standard treatment for myasthenia gravis and several other related muscular disorders.

In the area of neuroradiological examination of the nervous system the techniques for visualizing the vessels in the spinal cord in both tumors and trauma have been developed in large part in our laboratories at Bethesda and are now being used standardly by——

Mr. FLOOD. Great thing, that is right.

You will probably think of some others and your staff will later on, and supply those for the record.

Dr. TOWER. Yes, sir, we will.

[The information follows:]

OTHER SIGNIFICANT DIAGNOSTIC AND TREATMENT TECHNIQUES

(1) Alternate-day steroid therapy for myasthenia gravis.

(2) Acetazolamide (Diamox) treatment for hypokalemic periodic paralysis.

(3) Developed lactate infusion method for diagnosis of myasthenia gravis which is safer than the generally used curare test for evoking myasthenic weakness.

(4) Extended diagnostic use of the muscle biopsy by devising histochemical criteria for identifying various myopathies and neuropathies.

(5) Contributed information leading to development of computerized axial tomography for diagnosis and monitoring in head injuries, stroke, and brain tumors.

(6) Identification of high spinal-fluid measles antibody titers as a diagnostic test for subacute sclerosing panencephalitis thus replacing brain biopsy as a diagnostic method.

(7) Developed serologic diagnostic test for cytomegalovirus and Herpes I and II infections.

(8) Developed methods for activating paralyzed muscles in patients with quadraplegia; supported development of bladder evacuation prosthetic device for use by spinal cord patients.

(9) Introduced peripheral decarboxylase enzyme inhibitors (carbidopa) as a potentiator of the therapeutic effects of L-Dopa in Parkinson patients.

(10) Developed clinical tests to rigorously confirm the diagnosis of 10 sphingolipidoses including Gaucher's, Tay-Sachs, Neimann-Pick and Fabry's disease, based upon unique enzyme defect occurring in each disorder.

(11) Developed tests suitable for the prenatal detection of fetuses at risk for developing one of various sphingolipidoses and tests to detect carriers of these disorders.

(12) A new antiepileptic drug—carbamazepine (Tegretol).

(13) Use of anticoagulants in treatment of stroke.

(14) Development of noninvasive techniques for measuring cerebral blood flow.

(15) Use of hypothermia in the treatment of acute injury to central nervous system.

(16) Use of corticosteroids in the treatment of acute injury to central nervous system.

Mr. FLOOD. Thank you very much.
Mr. Natcher?

MUTIPLE SCLEROSIS MEETING IN SOVIET UNION

Mr. NATCHER. Doctor, I notice in your statement that you advise the committee that you will make a trip to the Soviet Union to discuss with Soviet counterparts matters concerning multiple sclerosis. What advancement have they made in the Soviet Union that we have not made in this country?

Dr. TOWER. Sir, I don't know that they have made any. That is one reason we are going to find out. But the principal reason is that the Soviet Union represents one of the few geographical situations in the world where they have extensive climatic differences and a large enough population spread with different ethnic, racial and cultural backgrounds that we could get some better clues with regard to the curious geographical distribution of multiple sclerosis. As you may know, multiple sclerosis is more concentrated in temperate and colder climates than it is in tropical climates. Somehow this must provide us with a clue to the cause of multiple sclerosis. What we would like to know is whether the Soviets have made a sufficient study of this problem.

This has been discussed with them before so that we hope they have the information now so that we can jointly take advantage of the situation. We are taking with us an epidemiologist for this particular purpose.

CLIMATIC CONDITIONS

Mr. NATCHER. Doctor, you also point out that in the Orkney and Shetland Islands the incidence of multiple sclerosis is the highest in the world. Climatic conditions to any degree? You pointed out in your answer to my previous question matters concerning temperate and colder climates.

Dr. TOWER. Climate is pretty severe in the Shetland and Orkney Islands but I don't know that is the only reason. Because the incidence is so high we have an epidemiologist under contract now over there making a survey to try and turn up what factors may be peculiar and common to those who have it or don't have it.

This is a standard technique when we don't know the answers and we find these clusters or foci around the world.

VIRUSES AND M.S.

Mr. NATCHER. Doctor, further in your justifications you state to the committee that many investigators believe that as far as multiple sclerosis is concerned, it may be triggered by a virus.

Dr. TOWER. Yes, sir.

Mr. NATCHER. We hear that real often and especially in regard to cancer and a lot of other matters. Doctor, that is not just as a matter of shield or something to get behind, is it? When you say a virus, you know, we hear so much about that it is probably from a virus.

Dr. TOWER. No, sir.

Mr. NATCHER. And in all of the serious and dread diseases it may be from a virus. Do you have anything to base that on as far as multiple sclerosis is concerned?

Dr. TOWER. I certainly do, Mr. Natcher. The circumstantial evidence is very strong that a virus is involved in multiple sclerosis.

We know, for example, that the multiple sclerosis patient has a much higher antibody relationship both in his blood and brain tissue to measles virus and in some cases to influenza virus than one normally encounters in the population. We also know that there are certain other disorders of the nervous system in which the measles virus in a defective form produces a demyelinating condition which is very similar to multiple sclerosis. We can produce this in animals, so we have a lot of circumstantial evidence to indicate this is so.

Furthermore, we know we can reproduce multiple sclerosis in animals by an immunological technique utilizing antibodies to the animal's own nervous tissues.

We suspect what may be the case in multiple sclerosis is that the virus infects certain people who for one reason or another have an extra susceptibility to it. They produce antibodies of their own which destroy their own tissue, whereas normally in you and me we would take care of it by the ordinary defense mechanisms that our bodies have.

So this is what we mean by a virus cause for multiple sclerosis. It is much more complicated than something like the common cold or polio or regular measles. That is why it is so difficult to find the answer, but we think we are well on the way to that. I wouldn't like to predict when the answer will come, but it is going to come a lot sooner than we thought a few years ago.

Mr. NATCHER. Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Michel.

MAJOR RESEARCH ADVANCES

Mr. MICHEL. Dr. Tower, certainly in its 25 years of existence, what is now the National Institute of Neurological and Communicative Disorders and Stroke, has contributed greatly to the research efforts in this area and I would laud the Institute on its accomplishments. If we might, could you give us a little "sneak preview" of what your forthcoming anniversary publication will highlight? What do you feel has been the major breakthrough in neurological and communicative research over the past 25 years?

Dr. TOWER. Thank you, Mr. Michel. We are grateful for the compliment you pay our Institute. Our anniversary publication is intended to span the entire field of neurosciences in which the Institute, has been interested during the past 25 years. More than 180 leading authorities in the basic and clinical neurosciences and communicative sciences have contributed chapters on topics ranging from neuropharmacology and neuroimmunology to medical treatment of epilepsy and Parkinson's disease to diagnostic audiology and acquired congenital hearing defects, to name just a few. It will highlight research advances and predict future directions research may take.

Major research advances during those years include development or discovery of:

One. The discovery that viruses are the cause of certain kinds of neurological degenerative diseases, notably the presenile dementias.

Two. Computerized axial tomography, an effective noninvasive scanning technique for diagnosis and monitoring of head injuries, stroke, brain tumors, and other disorders.

Three. Precise identification of specific enzyme defects associated with hereditary metabolic diseases affecting the CNS, such as phenylketonuria, galactosemia, and the group of sphingolipid storage diseases.

Four. Neuroradiologic diagnostic techniques including pneumoencephalography via the ventricular or spinal route and use of radiopaque dyes for myelography and angiography to visualize the spinal canal and the cerebral blood vessels, respectively.

Five. Electromyography for diagnosis of muscle and peripheral diseases.

Six. Radioisotope scanning techniques for diagnosis of brain tumors and other CNS lesions.

Seven. Control of nervous system infections such as meningitis and bacterial and fungal CNS infections including those associated with neurosyphilis and TB.

Eight. Sabin and Salk vaccines for eradication of acute polio.

Nine. Ergotamine treatment for migraine-type headache.

Ten. Surgical techniques to treat aneurisms of cerebral blood vessels and of occluded cerebral arteries.

Eleven. Copper restriction as dietary control of Wilson's disease.

Twelve. Cure of pernicious anemia with associated subacute combined degeneration of the spinal cord using vitamin B_{12}.

Thirteen. Development of diagnostic tests using small samples of blood to detect patients and carriers of the various sphingolipid storage diseases and to permit identification of the fetuses at risk during pregnancy so that genetic counseling can be available to the prospective parents.

Mr. MICHEL. A number of private groups have interests in this work and, in fact, promote nationwide fund-raising activities in several different areas. Do you have any figures on how much money is spent annually by private concerns?

Dr. TOWER. We are working with some 30 voluntary health agencies which have primary interest in neurological and communicative disorders. Each year they raise more than $100 million to be used for research, education, and special services for persons who have these disorders.

RESEARCH COORDINATION

Mr. MICHEL. How do you coordinate your efforts with private agencies and researchers?

Dr. TOWER. Here at the Institute every effort is made to coordinate our research program with private agencies and researches. In January 1975, we brought together at Bethesda representatives from virtually all the professional societies and voluntary health agencies in the fields of neurological and communicative disorders. Over 60 organizations and more than 100 representatives attended. As a result, there is better acquaintance with the NIH and the NINCDS, a realization of the need for greater coordination and cooperation rather than

a fragmented or individual approach, and an opportunity for the many organizations to get to know each other.

A number of our top professional staff members are on the medical advisory boards of many of the large voluntary agencies. As various state-of-the-art studies are made and research areas are reviewed, consideration is given to all research being supported by private agencies as well as government agencies. In relation to the individual grantee, researchers are asked to state specifically the source of their research support on all grant applications. The total research program of each grantee is then reviewed by NIH study sections as each grant is considered. This review is again made by the Institute's National Advisory Council.

FUNDS SPENT BY FEDERAL GOVERNMENT

Mr. MICHEL. What other Government agencies outside of NIH are involved in related research? Do you have a figure as to the total amount of money being spent by the Federal Government in this field?

Dr. TOWER. The Government agencies involved in research related to the nervous and communicative disorders are:

1. National Science Foundation.
2. Rehabilitation Services Administration, DHEW.
3. PHS Alcohol, Drug Abuse and Mental Health Administration.
4. PHS Center for Disease Control at Atlanta.
5. PHS Food and Drug Administration.
6. National Center for Health Statistics.
7. PHS Health Services Administration.
8. Office of Education.
9. Department of Defense.
10. National Aeronautics and Space Agency.
11. Atomic Energy Commission (previous title).
12. National Bureau of Standards.

We do not have a figure for the expenditures of these agencies for research in the neurological and communicative disorders. However, NIH funds support 40 percent of the Nation's health research and development as compared with 25 percent by other Federal agencies. If we extrapolate these percentages to the 1975 budget then we would estimate with $142 million for NINCDS plus $88 million for others a total of $230 million.

Mr. MICHEL. You say you will accompany a team of U.S. scientists to the U.S.S.R. in May. How does the incidence of multiple sclerosis in the U.S.S.R. compare to our own?

Dr. TOWER. As far as we know, it is comparable. However, there are low incidence foci, for example around Irkutsk in Siberia, where we would expect the incidence to be quite high. The size and geographical situation of the U.S.S.R. provide potentials for significant epidemiological correlations.

Mr. MICHEL. What kind of a research program have the Soviets developed in this area?

Dr. TOWER. We are not sure. Hence the reason for the trip under the United States-Soviet exchange program. This trip is in response to

one of the recommendations by the National Advisory Commission on Multiple Sclerosis.

Mr. MICHEL. Are we coordinating with any other countries in this or any related research?

Dr. TOWER. Yes; largely through the International Federation of Multiple Sclerosis Societies in liaison with the U.S. national society with which we maintain close continuing contacts.

FUNDAMENTAL NEUROSCIENCES

Mr. MICHEL. In regard to fundamental neuroscience in the areas of central nervous system regeneration and neuroimmunology, you state that "these are truly frontiers where spectacular advances may be expected in the next few years." Just what kind of advances can we expect? Are we talking about something as spectacular as a cure or what?

Dr. TOWER. Both of these fields are moving, gaining momentum, so that I anticipate some very real progress along broad fronts. The circumstantial evidence concerning central regeneration is sufficiently strong, as I have already indicated earlier, that we may expect certainly the demonstration in experimental animals of regeneration within a few years. The transition to paraplegic or stroke patients will inevitably be slower and more difficult. It would be unfair to speculate about cures yet, but surely the picture is much different than just a couple of years ago when experts concurred that central regeneration was not possible.

From neuroimmunology I think the answer may well be affirmative in several cases. The quantum jump from the days of a polio vaccine to the present era of cellular immunity, T and B lymphocytes, transfer factor, immuno-suppressive therapy, defective virus particles, and the like is a breathtaking advance. Since altered or impaired immuno mechanisms are involved in a number of neurological disorders, the present and inevitable future progress on these problems will certainly bring new or better therapies and eventually may even lead to some cures. Let me caution that the latter are likely to be far down the road, but again the whole picture is much, much brighter than a few years ago.

Mr. MICHEL. In the area of information, how well versed is the medical profession generally in the problems of neurological or communicative disorders? How has your Scientific and Health Reports Office approached this problem and what success have they had?

Dr. TOWER. The medical profession generally is quite well versed on the well known neurological and communicative disorders which can effectively be treated by drugs, such as L-Dopa for Parkinson's disease. They are much less well informed on rare neurological or communicative disorders, particularly complex diagnostic and therapeutic techniques.

The Scientific and Health Reports Office has an extensive program to solve this problem and I believe they are being increasingly successful. As an example, in the area of neuromuscular disorders, they have produced 28 video tapes which present the latest information on diagnosis

and treatment. In this past year we have had over 1,200 requests for these tapes from medical schools, Veterans' Administration and military hospitals, non-Federal hospitals, medical groups, and physicians. And there is already a long waiting list.

They have now prepared 15 video tapes on multiple sclerosis as a result of a recent workshop on progress in that area and there are plans for other tapes in the area of communicative disorders. This has been a pioneering approach by our Office of Scientific and Health Reports and we are proud of the results.

The Office is continuing the preparation and distribution of pamphlets for patients and physicians to provide them with the salient features and research progress in the various neurological and communicative disorders. Monographs presenting research studies have been distributed to research scientists and physicians. Radio spot announcements have allerted the public to treatment available and research underway for many disorders.

In an effort to cooperate more fully with the Department's regional offices, a program was initiated on an experimental basis to provide one of the regions with information on various clinical problems in forms suitable for dissemination to practicing physicians.

Workshops for research scientists and physicians have been held to review the state of the art in spinal manipulative therapy and in cochlear implants. One is planned in the near future to review the problem of autistic children.

Last January, representatives of 60 voluntary health agencies and professional societies met with Institute officials to review the status of research in the major neurological and communicative disorders. Through these organizations, as well as through the various media, research results have been disseminated to physicians, research scientists, and the public.

Mr. MICHEL. Thank you.

Mr. FLOOD. Mr. Conte?

PERCENTAGE OF POPULATION AFFECTED

Mr. CONTE. What percentage of the population is affected by the diseases under investigation of your Institute?

Dr. TOWER. Approximately 20 percent of the U.S. population.

INCIDENCE AND PREVALENCE

Mr. CONTE. Would you provide, if you have not done so already, a list of diseases into which you conduct research, along with their incidence in the population.

Dr. TOWER. The Institute is responsible for research into some 200 neurological and communicative disorders. The incidence and prevalence of some of the better known of these disorders will be supplied for the record. Since these are not reportable diseases, these figures will be estimates and will be based on figures supplied by voluntary health agencies and various studies relating to specific disorders:

[The information follows:]

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	Incidence (attack rate per year)	Prevalence (estimated total cases at any given time
Amyotrophic lateral sclerosis	2,846	10,000
Cerebral palsy	15,000	750,000
Epilepsy	60,990	2,000,000
Head injuries	3,000,000	1,600,000
Huntington's		Over 14,000
Hydrocephalus	1 in every 2,000 births	
Multiple Sclerosis	75,000 to 100,000 persons with clinically identifiable multiple sclerosis.	Over 250,000
Muscular dystrophy		200,000
Myasthenia gravis	6,096	100,000
Parkinson's	40,640	200,000
Spina bifida	11,000 babies are born annually with spina bifida or related birth defects.	27,500
Spinal cord injury	10 to 12,000 new civilian paraplegics each year	125,000
Strokes	500,000 to 600,000 new or recurrent	2,000,000
Tay-sachs	50	250
Hearing impairment deaf		2,000,000
Partial hearing loss		11,500,000
Speech impairments		10,000,000

Mr. CONTE. Can you estimate the cost of neurological disease to society, in terms of both medical costs and work loss?

Dr. TOWER. The cost for medical and related care is estimated at about $20 billion annually. The cost in work loss and related aspects is not accurately known. We are conducting several surveys to obtain selected data in this area. What few data are available indicate these costs to be at least equal to the care costs.

COMMUNICATIVE DISORDERS

Mr. CONTE. Last year you told us about the research manpower shortage in the area of communicative disorders? Has that situation improved or worsened over the past year? What do you intend to do this year to deal with that situation? Does this budget provide adequate manpower to safeguard the supply of researchers in this area?

Dr. TOWER. The communicative disorders include the research areas of disorders of hearing, speech and language. Research manpower needs require personnel trained in: the medical disciplines of otolaryngology and neurology; the clinical disciplines of audiology and speech pathology; and in the basic sciences the disciplines of biophysics, microscopic anatomy, sensory physiology, virology and epidemiology. Each of these research disciplines is one of short supply nationally, and particularly as these skills address the problems of the communicative disorders. During fiscal year 1975, the NINCDS programs of individual and institutional research fellowships were aimed specifically at arresting the steady decline of research personnel in these shortage areas. In fiscal year 1976, the NINCDS manpower training programs will continue the already active fellowships initiated last year. We will be able to support 14 graduate training grants, 39 National Research Service awards, and 5 research fellowship awards.

EPILEPSY

Mr. CONTE. Have there been any new drugs developed in the past year to control epilepsy? This year? Are any in the clinical stage of testing?

Dr. TOWER. In 1974, Tegretol (carbamazepine, Geigy) was approved by the FDA for use in epilepsy. This was the first drug with the major indication of epilepsy to be approved since 1960. NINCDS-sponsored clinical studies were included in the New Drug Application submitted to the Food and Drug Administration by Geigy. In 1975, Hoffmann-LaRoche will market Clonopin (clonazepam) another new drug for use in epilepsy. NINCDS clinical studies were also included in this New Drug Application. We are aware of four investigational drugs in various stages of clinical evaluation for anti-epileptic activity. The most interesting of these is Depakane (dipropylacetic acid sodium, Abbott). We are involved with the clinical evaluation of each of these four agents.

Mr. CONTE. Last year at this time you were about to embark on the feasibility stage of a comprehensive epilepsy program. What stage are you in now? Where do you go from here?

Dr. TOWER. Eleven 1-year feasibility studies were funded last year. These studies were selected to represent urban, rural, and rural-urban populations. On the basis of quarterly reports from these centers, each is progressing well. Based upon our desire to further develop the comprehensive epilepsy program concept, the Institute advertised for research contracts to conduct comprehensive epilepsy programs. Responses were not limited to those 11 feasibility contractors, but competition was open to all interested organizations. Contractor's proposals are due at NIH on April 21, 1975. They will be reviewed by an ad hoc Technical Merit Review Committee, and the Institute will fund at least one comprehensive program this fiscal year.

MULTIPLE SCLEROSIS

Mr. CONTE. Would you tell me what has been done in the past year to implement the recommendations of the National Advisory Commission on Multiple Sclerosis?

Dr. TOWER. The report of the National Advisory Commission on Multiple Sclerosis was presented to the Secretary (HEW) in February 1974 and was well received. Since that time, several thousand copies of the report have been distributed to scientists, Members of Congress, and the public on request. The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) has studied the recommendations, has indicated its general concurrence, and has implemented many of the recommendations.

As suggested by the Commission, an Institute staff scientist has been designated as the focal point for multiple sclerosis. Dr. John L. Sever is personally involved in multiple sclerosis research, is Chief of the Infectious Diseases Branch, Intramural Research, and presently heads the Institute's Multiple Sclerosis Task Team of NINCDS scientists.

In February 1975, Dr. Sever conducted a workshop on "Perspectives in Multiple Sclerosis—1975." Fifty scientists participated in presenting recent advances in immunology and virology which relate to multiple sclerosis. Abstracts of the papers presented will appear in the May issue of Neurology. Video and audio tapes are available for almost all papers.

The Commission recommended a total of 5 multiple sclerosis clinical research centers. Two were funded by the Institute at UCLA and

at the University of Pennsylvania-Wistar Institute, prior to the Commission's report. This past year another multiple sclerosis research center has been funded at Emory University, Atlanta, and two more centers will be funded before July 1975.

The Commission recommended various epidemiological studies of the disease. Two contracts have now been negotiated. One of these relates to the Shetland-Orkney Islands where there is a high incidence of multiple sclerosis. The other is a nationwide survey of the prevalence and cost of multiple sclerosis.

The Commission recommended that the Institute underwrite major programs in virological research, and promote major research into immune mechanisms. The Institute has had a strong virological research program which it is expanding. Recently, two contracts dealing with physical and biochemical methods for study of multiple sclerosis tissues for viruses, biochemical changes, and immunological reactions have been awarded. At the Institute's Bethesda laboratories, a new laboratory of neuro-immunology has been established. Special training and fellowship programs in neuro-immunology and neuro-virology also have been inaugurated.

Some of the recommendations, such as developing specific diagnostic tests, establishing mechanisms for providing fresh tissue samples, and promoting various approaches to therapy will take time to develop.

The extent to which some of these developments take place depends upon availability of funds and scientific interest. Recent developments on each of these is now positive. This has been shown in the wide interest of scientists in the recent Perspectives in Multiple Sclerosis workshop. Also, the Institute's budget, as finally approved by Congress and the President, will make possible the increase in multiple sclerosis research for the current fiscal year recommended by the Multiple Sclerosis Commission.

VIRAL INFECTIONS

Mr. CONTE. There was an article in the March 11 New York Times concerning the transmission of Creutzfeldt-Jakob Disease virus through a corneal transplant. What sorts of safeguards are in effect to prevent transplant-related transmission of viral infections?

Dr. TOWER. Such sources of infection have been widely publicized in both professional journals and in the public press. There are no absolute safeguards because of the very long incubation period of such diseases and the lack of screening tests during the latent phase. Our scientists have strongly advised against use of transplants from any patient with suggestive family histories or with any neurological signs or symptoms, as well as any patients who are on or have been on immuno-suppressive therapy.

Mr. CONTE. How many neurological diseases may be viral in origin, and which ones?

Dr. TOWER. The potential number is very large. Those for which the probability of viral origin is high include: presenile dementia group, multiple sclerosis, amyotrophic lateral sclerosis, some forms of epilepsy and Parkinson's disease.

Mr. CONTE. The New York Times article suggested the possibility that virus-caused neurological disease might be a professional hazard

of surgeons and pathologists who handle brain tissue. Do you consider this likely, and if so, do you have any suggestions for getting around this problem?

Dr. TOWER. Yes, we consider this a definite potential hazard. Our scientists have published warnings in the Journal of Neurosurgery and elsewhere and have strongly recommended strict aseptic precautions as with any infectious material.

RESEARCH ON SLOW AND LATENT VIRUSES

Mr. CONTE. Would you outline the progress and work going on in research into latent and slow viruses?

Dr. TOWER. The demonstration by NINCDS scientists that kuru, a heredofamilial disease, and Creutzfeldt-Jakob disease, a presenile dementia, are both transmissible diseases caused by viruses with atypical properties has provided the techniques and impetus for the study of other central nervous system diseases. It has now been clearly established that many "slow-infections" of the central nervous system of man are caused by "conventional viruses," that is viruses which possess a definable nucleic acid type, which can be visualized by electron microscopy, which induce specific antigen-antibody reactions and which are easily destroyed by physical and chemical treatment in vitro and by "unconventional viruses," that is viruses which have not thus far been shown to possess nucleic acid, which do not induce an immune response, which have not been visualized by EM and which are highly resistant to most physical and chemical treatments known to be capable of inactivating most viruses.

Notable examples of the first group are: Subacute sclerosing panencephalitis caused by defective measles virus, progressive multifocal leucoencephalopathy, from cases of which two papovaviruses designated JC virus and SV40-like virus have been isolated, and chronic encephalitis caused by tick-born virus. Although a viral etiology has not yet been proven by isolation of the virus, sufficient immunological, histopathological and epidemiological data exist to support a probable viral etiology for multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, and additional forms of chronic encephalitis with focal epilepsy. These data support the strong possibility that such diseases will be due to "garden-variety type" conventional viruses.

Indeed, within recent months NINCDS supported investigators in California have described an SSPE-like fatal illness in 5 children in which rubella—not measles virus—was determined to be the etiological agent.

Recent seroepidemiological surveys by NINCDS scientists on sera collected from primitive and nonprimitive populations in the world show widespread distribution of antibody to the JC and SV40-like viruses of PML. The high incidence of antibodies to these viruses in young children strongly supports the hypothesis that these are rather ubiquitous viruses which infect man at an early age, and which remain latent until reactivated, by as yet unknown mechanisms, to cause fatal central nervous system disease.

The atypical and unconventional viruses of kuru, Creutzfeldt-Jakob disease, scrapie and transmissible mink encephalopathy are proving

to be the most challenging biological entities in the field of infectious diseases. Major emphasis has been placed on procedures to purify the infectious agent, determine their physical and biological characteristics and arrive at working hypothesis as to the nature of these infectious agents. NINCDS scientists, working in collaboration with their colleagues in several laboratories in the United States and abroad, have recently shown that these viruses are inextricably associated with the unit or plasma membranes of cells in the central nervous system. The basic structure of these membranes is altered in such a manner as to suggest fragmentation and abnormal growth with invagination into vacuoles within the axonal and dendritic processes of cells. Indeed, brains of animals inoculated with kuru show specific cellular abnormalities as early as 1 month, for example binucleation of neurons, status spongiosis, and so forth. These findings have been confirmed by the detection of altered brain waves in EEG studies as early as 4 months after inoculation. Purification data strongly suggest that infectivity of the viruses is associated with a high ratio of protein to nucleic acid (RNA) even though it has thus far not been possible to isolate and identify a specific nucleic acid.

Recent studies have now shown that both the sporadic and familial types of CJD are transmissible. There has also been a conjugal occurrence with about the same incubation period in both patients suggesting a common exposure. Most interestingly NINCDS scientists have recently transmitted two independent cases of familial Alzheimer's disease to squirrel monkeys.

Finally, it is most significant to note that scrapie virus has been adapted to primates inoculated with infected tissues from sheep, goats and mice. Once the virus has been into primates it no longer is capable of inducing disease in mice. The precise alteration is not known. Since kuru and CJD viruses have not induced disease in sheep it may well be that the sheep diseases—scrapie—is not innocuous for man. Attempts to induce scrapie disease in sheep and goat inoculated with primate-adapted scrapie as well as kuru and CJD human tissue are being conducted in collaboration with scientists at the U.S. Department of Agriculture.

LABORATORY OF NEUROIMMUNOLOGY

Mr. CONTE. Would you give me a progress report on the creation and staffing of the Laboratory of Neuroimmunology? What part of your budget will go to the support of this Laboratory? Could you describe the work which will be carried out there?

Dr. TOWER. Dr. Dale McFarlin has been selected as the Chief of this Intramural Laboratory. His space is being renovated, and basic equipment ordered. We have also made tentative selections of key staff members. The Laboratory should be in full operation early next year. The operating budget for this Laboratory will be about $325,000, with 11 employees. The work will involve:

A. BASIC INVESTIGATIONS

(1) Develop techniques and assays to characterize the immune response to agents such as measles which cause chronic CNS disease. (2) Characterize the effect of infection upon the host. For example,

measles infection suppresses immunity. (3) Characterize surface membrane components of nerve cells, glia and myelin using immunological techniques.

B. CLINICAL INVESTIGATION

The assays will be used to study patients with neurological diseases. The immune response against virus and CNS antigen will be studied in chronic CNS diseases of unknown etiology, such as amyotropic lateral sclerosis, multiple sclerosis, and possibly brain tumors.

FREDERICK CANCER RESEARCH CENTER

Mr. CONTE. During the past year your facility at the Frederick Cancer Research Center was supposed to be brought on line. Was it? What is the nature of your cooperation with the National Cancer Institute? How do you avoid duplication and overlapping of work?

Dr. TOWER. In November 1973, the laboratory concerned with slow, latent and temperate viruses was transferred from the Patuxent Wildlife Research Center, Laurel, Md., to building 567, Frederick Cancer Research Center, Fort Detrick, Md. No significant time was lost to the program activities and the transition was well coordinated and efficiently carried out. Since initial occupancy additional rooms within building 567 have undergone minimal remodeling to provide space for the initiation of experimental studies which had been delayed due to inadequate space at Patuxent. Building 376, the permanent NINCDS facility is currently undergoing internal demolition and reconstruction is to begin later this summer and will take about 10 months to complete.

There is a close working relationship between the scientists in NINCDS and NCI. Many of the basic techniques and reagents developed and produced by scientists of NCI for detection of virus genetic information in living cells and for the identification and characterization of oncogenic viruses are now being used by scientists in NINCDS for studies of the central nervous system. Human brain cells from a patient dying with Creutzfeldt-Jakob disease spontaneously transformed in the laboratory and NINCDS scientists were able to isolate a virus from these malignant cells which was later characterized by NINCDS–NCI scientists as a "C" type particle with morphological and immunological characteristics of oncogenic viruses.

Purification studies have now clearly shown this virus to be antigenically related to a virus which causes breast tumors in subhuman primates; the virus has no etiological significance in Creutzfeldt-Jakob disease. More recently the same NINCDS–NCI scientists have isolated three additional "C" type viruses from gibbon apes, in the "slow virus" program, which are related to the virus isolated by NCI scientists from human patients with leukemia. Many of the basic concepts of virus-cell interaction in slow infections of the nervous system that have been and are being developed by NINCDS scientists working in this discipline are assisting NCI scientists in their understanding of the mechanisms of pathogenesis of disease caused by oncogenic viruses.

Avoidance of duplication and overlapping of work has thus far been achieved by establishing close collaborative studies which utilize the scientific capabilities of the two groups. Indeed, until recently many of the techniques of molecular biology had not been fully implemented

into studies on the central nervous system. With the intramural program NINCDS scientists are now adapting these techniques to the study of the central nervous system in an effort to detect with greater sensitivity viral genetic information in normal and diseased tissues.

NUMBER OF APPROVED UNFUNDED GRANTS

Mr. CONTE. How many approved grants do you expect will be unfunded in 1976? How does this compare to 1975 and 1974?

Dr. TOWER. We estimate that 1,033 approved research grant applications, totaling $53,971,000, will be unfunded in 1976. This figure includes 319 noncompeting grants for $16,454,000. In 1975, comparable data are 238 approved applications unfunded, totaling $12,536,000, and in 1974, the figures were 439 applications and $17,478,000.

Mr. CONTE. What is the projected average cost of new grants for 1976? How does this compare to 1975 and 1974? What accounts for the difference?

Dr. TOWER. The average cost of approved new research grants has increased from $55,536 in 1974, to $56,414 for 1975, and $56,948 for 1976. Three principal reasons account for this increase: (1) the steadily increasing costs nationally of personnel, equipment and supplies; (2) the increased need for sophisticated and usually expensive equipment required for the quantitave measurements now available for research, and (3) increased emphasis on clinical research requring reimbursement for research patient costs.

Mr. CONTE. Would you tell me how your Institute and the National Heart and Lung Institute divide responsibility for stroke research?

Dr. TOWER. There are two aspects of stroke research: research on the brain and its circulation and research on the blood vessels and their contents. The NINCDS has primary responsibility for research on the factors that regulate the microcirculation of the brain; the transfer of oxygen and glucose to the brain cells and the removal of metabolic waste products; the effects on brain cells of lack of oxygen and glucose; the development of methods of preventing stroke and of protecting the brain during stroke; the devising of improved techniques of stroke diagnosis; and the development of reliable methods of stroke treatment. The NHLI has primary responsibility for research on atherosclerosis, hypertension and blood factors that cause blocking of blood vessels, and on disorders of the heart that diminish circulation. The research efforts on stroke of the two Institutes are coordinated by continuing staff and consultant joint planning.

HEAD INJURY RESEARCH

Mr. CONTE. Last year you said that you would look into the development of research on head injuries in conjunction with the emergency medical services (EMS) program. Has anything been done on this?

Dr. TOWER. Traumatic injuries to the head and spinal cord often result in death or paralysis unless the immediate effects of the injury can be arrested or reversed. This requires rapid diagnosis and almost immediate medical attention. By means of its program of head injury clinical research centers and acute spinal cord injury clinical research centers, a national network of nervous system trauma centers is being

established. These centers are all integral parts of the regional programs of emergency medical services including roadside services, helicopter transportation and hospital triage. In addition, these acute care clinical centers also are integral parts of regional rehabilitation systems so that victims of central nervous system injuries can initiate remedial activities that will increase their potential when they return to the community. Thus, the NINCDS supported head and spinal cord injury clinical research centers serve as regional focal points in the emergency medical services systems for the development of improved clinical services to those with trauma to the central nervous system.

EFFECT OF BUDGET REDUCTION

Mr. CONTE. Last year, in response to questioning, you told how much work needed to be done by your Institute. You told us how much there was to be discovered in the neurological area, and how necessary this type of research was. Now you are here with a budget which projects obligations which are 19 percent lower than the 1975 appropriation. Can you explain this decrease? Are you serious, or are you depending upon your friends on the committee to raise this amount?

Dr. TOWER. As you know, the Congress appropriated, and the President concurred in our obligating $142.5 million for 1975. We were given an allowance of $114.9 million for 1976. We will still be able to run a good program with this amount. However, we will necessarily have to make substantial, perhaps across-the-board reductions in program activities, and even terminate some projects entirely. If increases are allowed, I know we can continue with additional worthwhile and necessary projects.

Mr. CONTE. This year you are planning to award about 400 fewer grants than last year, for about $13 million less money. What effect will this have on progress toward solving the problem of stroke and other neurological-related diseases?

Dr. TOWER. The proposed reduction in research grant funding in 1976 will be accomplished by decreasing the rate of research activity in stroke and other neurological diseases and the discontinuation of selected ongoing research activities of lesser priority. This will result in a slowing of progress.

Mr. CONTE. There seems to be a decrease everywhere in your justification except in departmental management. Can you justify your management increase in light of the cuts in research funding?

Dr. TOWER. Administrative costs such as pay raises, operating expenses for facilities, telecommunications and postage, increased costs for supplies and equipment, both for the Institute and in the NIH's management fund, continue to rise, and thus account for these increases.

TRAINING PROGRAMS

Mr. CONTE. You are proposing a cut in training grant support, in favor of an increase in fellowship support . This may be a good idea, but I wonder if you could provide some of the background and reasoning that went into the decision to phase out training grants in favor of fellowships?

Dr. TOWER. The "old" training grant program, now in the final phases of its phaseout, was aimed at the development and improve-

ment of academic training environments and the support of selected trainees. The training grant provided funds for the salaries of teacher-investigators and training equipment so that all trainees would receive an adequate or even superior level of education in the basic or clinical science discipline of the grant; stipend support was provided only for those trainees for which local or other sources of funds were not available. The "new" program is aimed at the support of trainees in selected research areas of national need with modest overhead expenses to the training institution. Thus, the change was that of supporting the trainee rather than the trainer and the training environment. The assumption behind this NIH-wide change is that other sources of funds are available now for support of the training environment.

HEARING AIDS

Mr. CONTE. Your justification refers to the development of a master hearing aid. What does this do, and how is it an improvement over previous hearing aids?

Dr. TOWER. The wearable master hearing aid is a miniaturized research device that packages a small psychoacoustics laboratory into a size and weight that may be worn comfortably by a hearing impaired person engaging in everyday activities. This device allows many features of the device's acoustic characteristics—such as frequency bandwidth, slope of response, compression onset/offset time, and so forth—to be varied independently to achieve the best individual fit. The wearable master hearing aid is being used in research to develop improved procedures for fitting aids to persons who previously have not obtained satisfaction from commercially available aids.

LANGUAGE LEARNING

Mr. CONTE. You mentioned in your justification research into the critical age for language learning by children. Once you find out what it is, what are you going to do with it? What is the next step?

Dr. TOWER. The hypothesis of critical ages for language learning suggests that children who fail to achieve certain levels of language mastery because of inadequate language stimulation—which might be attributable to environmental influences or to sensory deprivation such as occurs in congenital deafness—will never achieve the level of mastery which would have been possible if language had developed at an earlier age. This hypothesis has important implications for educational programs in general and for hearing-impaired children specifically, but the available research literature contains conflicting information. The project investigating this hypothesis involves an interdisciplinary team of behavioral and biological scientists who are developing two documents which will review, synthesize, and criticize available research information concerning this hypothesis and which will discuss research strategies for answering important, related questions where information is lacking. Since both documents will be published in scientific journals, we expect them to encourage increased research attention to children's language problems as well as more technically sophisticated research approaches. We may also issue requests for proposals to conduct research which is well suited to the contract approach.

FREEZE-FRACTURE

Mr. CONTE. Would you describe the process of freeze-fracture electron microscopy? What distinguishes it, in process and results, from ordinary electron microscopy?

Dr. TOWER. Freeze-fracture is a technique for preparing tissue for ordinary electron microscopy. Tissue is processed by first freezing, then fracturing, and finally making a metal replica of its fractured surface. Tissue prepared this way can be examined closer to its natural state because the use of chemical preservatives, such as formaldehyde, is avoided. Fracturing the frozen tissue splits the membranes of cells, producing panoramic views of membrane interiors where extremely small structures the size of individual protein molecules can be seen. Visual pigments in the eye; attachments of individual viral proteins; and sites of receptors for drugs important in the function of the nervous system have been first seen with the freeze-fracture technique. Work is just beginning with this technique on the numerous pathological conditions and disease agents which affect the structures inside of membranes.

While the freeze-fracture technique is in theory simple, it requires stringent control of conditions during fracturing and replica making. The freeze-fracture apparatus must maintain the frozen tissue at −180° F. in a vacuum which is much higher than that required by an electron microscope. It must also contain a device for making metal coatings and a cutter which can fracture the tissue at exactly the right place. Because of the stringent vacuum and mechanical requirements, the cost of a freeze-fracture apparatus is high and averages one-half that of the electron microscope itself.

Mr. CONTE. In your justification, it says, and I quote: "The diseases of the human nerve system are among the most chronic, debilitating, costly, and least understood of all those that afflict man. Support in the fundamental neurosciences represents the investment by NINCDS in the problem areas * * *" and so forth. After all this talk about the importance of fundamental neurosciences, you have a $4 million decrease from last year. How can you justify this?

Dr. TOWER. Much of the fundamental research in the neurosciences is supported by the NINCDS as part of the other three program areas of Institute responsibility: Neurological disorders, stroke and neural trauma, and the communicative disorders. Only those areas of basic research not directly applicable to these targeted areas are included in the fundamental neuroscience program. Because of the lower budget proposed for fiscal year 1976, the Institute will have to decrease the fundamental neuroscience program proportionately, while providing for adequate basic and clinical research needs in the three clinically oriented research programs. Despite the anticipated reduction, a substantial program in the fundamental neurosciences will be maintained.

HUNTINGTON'S DISEASE

Mr. CONTE. Would you outline the level of support for your research efforts into Huntington's disease?

Dr. TOWER. Studies directly on Huntington's patients is at a level of $555,000. However, fundamental research studies in the fields relevant to the Huntington's disease problem total $4.9 million, and a

recent workshop has identified some promising new leads that will now be exploited.

Mr. CONTE. In your statement, you said that you are reorganizing your present extramural grant program into the four program areas. How will this work mechanically? In other words, is this simply an internal accounting change, or will it make a difference to your extramural researchers? What difference will it make?

Dr. TOWER. The reorganization of the NINCDS' extramural programs will result in our activities being program oriented rather than mechanism oriented. Instead of a grant program and a contract program, the NINCDS will now be organized into four program areas: Communicative disorders; neurological disorders; stroke and neural trauma; and fundamental neurosciences. Each program area will have a program manager who will be responsible for all grant and contract activities within the program area. Extramural researchers will now have one administrative organization to work with instead of two; the Institute will have a responsible manager for planning and coordination in each area. This administrative structure should provide for improved responsiveness on the part of our staff and increased Institute accountability.

NERVOUS SYSTEM REGENERATION

Mr. CONTE. In your statement you referred to fundamental neuroscience work in central nervous system regeneration and neuroimmunology. What leads you to believe that spectacular advances may be expected in the next few years? What kinds of advances?

Dr. TOWER. My opinions are based on the following recent developments. In the field of CNS regeneration, the National Advisory Council of the NINCDS last year set up a subcommittee to examine the current status of the field. Under auspices of our Council subcommittee a series of workshops have been held at which a wealth of information was discussed on nerve fiber—axonal—budding and growth, collateral sprouting, cell-to-cell recognition, formation of cell-to-cell connectors, and effects of hormones and nerve growth factor. In animal models, certain brain areas, deprived of normal innervation by ablation techniques, have been reinnervated by sprouting of collateral fibers from other nerve cells, a reinnervation proven anatomically by microscopic examination and functionally by microelectrode recordings. These various reports and observations provide strong circumstantial evidence in favor of the potential with brain and spinal cord for regeneration after injury or selective cell destruction. By publicizing these developments through investigator participation in the workshops and through publication of the proceedings, as well as by grant and contract promotion, we anticipate a surge of research in these areas. I am confident that the results will yield significant breakthroughs toward the solutions of such problems as the spinal-cord injured.

With regard to neuroimmunology, the recent advances along all fronts in immunology hold great promise for the many neurological and communicative disorders that result wholly or in part from disturbances in the immune defenses of the body. We know of clinical and experimental diseases of the central nervous system that result

from defective viruses. In the case of SSPE—subacute sclerosing panencephalitis—a fatal childhood demyelinating disease, it is a defective measles virus, but the normal bodily defenses have failed because of the presence of a circulating blocking factor which prevents the usual attack on and destruction of the virus-infected cells. In PML—progressive multifocal leukoencephalopathy—a demyelinating disease caused by viruses of the papova virus group, the onset of disease characteristically follows the use of immunosuppressive therapy, that is, at a time when the body's defenses are down. These examples illustrate some of the ways immunological mechanisms are important in neurological diseases. We are convinced that multiple sclerosis, amyotrophic lateral sclerosis, the kuru-scrapie-Creutzfeldt-Jakob disease group, myasthenia gravis, and others are partly or wholly results of alterations or defects in the immune responses of patients with these disorders. The advances in knowledge and increasing investigator interest in the field of neuroimmunology, with specific encouragement from the NINCDS grants and training programs, will, I am certain, produce real advances toward the solving of many of these clinical puzzles.

Mr. Conte. Thank you, Mr. Chairman.

Mr. Flood. Thank you, Doctor.

Dr. Tower. Thank you.

Justification of the Budget Estimates

Appropriation Estimate

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

For expenses necessary to carry out, to the extent not otherwise provided, title IV, parts D and I, of the Public Health Service Act with respect to neurology and stroke, [$142,498,000] *$114,955,000.*

For the "National Institute of Neurological and Communicative Disorders and Stroke" for the period July 1, 1976, through September 30, 1976, $28,739,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Amounts Available for Obligation 1/

	1975 2/ Estimate	1976 Estimate
Appropriation	$142,498,000	$114,955,000
Comparative transfer to:		
"Office of the Director, NIH" (Transfer of the Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	-44,000	---
"Research Resources" (for the rhesus monkey supply program)	-120,000	---
"Research Resources" (for Caribbean Primate Research Center)	-300,000	---
Total, obligations	$142,034,000	$114,955,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 $100,000; 1976 $100,000.

2/ Excludes 1973 restorations in the amount of $33,000.

Summary of Changes

1975 Estimated obligations	$142,034,000
1976 Estimated obligations	114,955,000
Net change	-27,079,000

	1975 Pos.	1975 Amount	Change from 1975 Pos.	Change from 1975 Amount
Increases:				
A. Built-in:				
1. Within grade salary increases	--	--	--	+$262,000
2. BEC rate change	--	--	--	+4,000
3. One extra day of pay	--	--	--	+44,000
4. FTS	--	--	--	+16,000
5. Increased cost of postage	--	--	--	+5,000
6. Service and supply fund	--	--	--	+200,000
7. Annualization of 1975 pay increase in 1975	--	--	--	+183,000
8. Payment to NIH Management Fund for centrally furnished services	--	--	--	+136,000
9. Wage board increases expected to be granted during remainder of 1975	--	--	--	+5,000
Subtotal	--	--	--	+855,000
B. Program:				
1. Research Grants:				
a. Non-competing from awards in prior years	--	$55,093,000	--	+33,808,000
b. Competing	--	33,808,000	--	+14,876,000
c. Scientific evaluation	--	205,000	--	+31,000
2. Fellowships:				
a. Non-competing from competing in prior years	--	529,000	--	+2,961,000
b. Competing	--	2,912,000	--	+900,000
3. Research and Development Contracts:				
a. Non-competing from competing in prior years	--	6,682,000	--	+3,378,000
b. Competing	--	3,378,000	--	+40,000
4. Research management and program services	--	3,088,000	--	+39,000
Subtotal	--	--	--	+56,033,000
Total, increase	--	--	--	+56,888,000
Decreases:				
A. Program:				
1. Annualization in 1976 for reduction of 3 positions	513	12,227,000	-3	-60,000
2. Research and development contracts:				
a. Completed	--	6,682,000	--	-771,000
b. Competing	--	3,378,000	--	-3,378,000

Summary of Changes (cont'd)

	1975 Pos.	1975 Amount	Change from 1975 Pos.	Change from 1975 Amount
Decreases:				
3. Research grants:				
a. Non-competing terminated..	--	55,093,000	--	-16,906,000
b. Competing.....	--	33,808,000	--	-33,808,000
c. Continuation costs generated in 1976 by the failure of the 1975 rescission request.....	--	55,062,000	--	-17,581,000
4. Fellowships:				
a. Non-competing terminated..	--	529,000	--	-290,000
b. Competing.....	--	2,912,000	--	-2,912,000
5. Training grants:				
a. Non-competing terminated..	--	9,582,000	--	-5,782,000
6. Laboratory and clinical research.....	--	13,458,000	--	-1,822,000
7. Collaborative research and support.....	--	6,059,000	--	-657,000
Total, decreases.....	--	--	--	-83,967,000
Total, net change.....	--	--	--	-27,079,000

Explanation of Changes

Increases:

A. Built-in:

1. The increase will provide $262,000 for within grade salary increases ($219,000 in intramural laboratory and clinical research and $43,000 in research management and program services).
2. The increase will provide $4,000 for the Bureau of Employee Compensation (BEC) rates (centralized for management purposes in intramural laboratory and clinical research).
3. The increase will provide $44,000 for one extra day of pay in 1976 ($37,000 in intramural laboratory and clinical research and $7,000 in research management and program services.
4. The increase will provide $16,000 for increases in Federal Telecommunications System (FTS) rates (centralized for management purposes in intramural laboratory and clinical research).
5. The increase will provide $5,000 for postage rate increases (centralized for management purposes in intramural laboratory and clinical research).
6. The increase will provide $200,000 for increased building rental cost and other miscellaneous costs, including service and supply costs ($160,000 for intramural laboratory and clinical research and $36,000 for research management and program services).
7. The increase will provide $183,000 for the annualization of 1974 pay raise cost in 1975 ($154,000 in intramural laboratory and clinical research and $29,000 in research management and program services).
8. The increase will provide $136,000 for increased cost of the NIH Management Fund for centrally furnished services, including $81,000 for annualization of the cost of the October 1974 pay raise.
9. The increase will provide $5,000 for annualization of wage board increases expected to be granted in 1975 (all to intramural laboratory and clinical research).

B. Program:

1. Research Grants:
   a. The increase of $33,808,000 in noncompeting grants represents the continuation costs of 572 previously awarded competing grants including 27 research career development awards. The net result is an increase of 297 grants; from 742 in 1975 to 1,039 in 1976. This increase of 297 includes 4 research career development awards; from 66 in 1975 to 70 in 1976.
   b. The increase of $14,876,000 is for competing research grants including special programs. The net result is a decrease of 383 competing grants, from 572 in 1975 to 189 in 1976. This includes research career development awards of 27 in 1975 and 25 in 1976.
   c. An increase of $31,000 is required for the review of research grants and fellowships.
2. Fellowships:
   a. The increase of $2,961,000 represents the continuation of 170 previously awarded competing fellowships.
   b. The increase of $900,000 is for 63 new competing NRSA fellowship awards.
3. Research and Development Contracts:
   a. The increase of $3,378,000 represents the continuation of 28 previously awarded competing contracts.
   b. The increase of $40,000 is for one new contract in 1976.
4. Research management and program services - This increase will support NIH and NINCDS program evaluation studies, the Institute's share of supporting DHEW and NIH research programs, and additional support for the NINCDS office of program planning and evaluation.

Decreases:

A. Program:

1. The reduction of $60,000 reflects the full year cost in 1976 of 3 positions eliminated; 3 in intramural laboratory and clinical research.
2. Research and development contracts:
   a. The decrease of $771,000 is a result of eight contracts completed or terminated after 1975.
   b. The decrease of $3,378,000 and 28 contracts is the amount for 1975 competing contracts that are not included in the base for 1976.
3. Research grants:
   a. The decrease of $16,906,000 is a result of 247 non-competing research grants that terminated after 1975. This includes 23 research career development awards.
   b. The decrease of 572 grants and $33,808,000 is the amount of 1975 competing research grants that are not included in the base for 1976.
   c. The decrease of $17,581,000 is the amount for 327 continuation costs of the lowest priorities which will not be funded. This includes 8 research career development awards for $177,000.
4. Fellowships:
   a. The decrease of $290,000 is a result of the phase-out of seven non-competing fellowships that terminated after 1975.
   b. The decrease of $2,912,000 is the amount of 1975 competing National Research Service Awards that are not included in the base for 1976. The number of awards was 170.

5. Training grants:
   a. This decrease of 112 grants and $5,782,000 represent those training grants that were phased-out or terminated after 1975.
6. Laboratory and clinical research - The decrease of $1,822,000 is for non-recurring requirements such as renovation and equipment for the new laboratories of neuroimmunology and of neuropharmacology and purchase of computerized x-ray scanning equipment.
7. Collaborative research and support - The decrease of $657,000 reflects the continuation of the phase-out of the collaborative perinatal program.

OBLIGATIONS BY ACTIVITY

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
241	Communicative Disorders.....	--	$ 16,840,000	--	$ 14,318,000	--	-$2,522,000
243	Neurological Disorders.....	--	62,688,000	--	47,060,000	--	-15,628,000
247	Stroke and Nervous System Trauma.....	--	17,396,000	--	14,303,000	--	-3,093,000
249	Fundamental Neurosciences.....	--	15,029,000	--	10,838,000	--	-4,191,000
251	Intramural Laboratories and Clinical Research.	421	25,777,000	418	24,006,000	-3	-1,771,000
254	Research Management and Program Services.....	92	4,304,000	92	4,430,000	--	+126,000
	Total Obligations.....	513	142,034,000	510	114,955,000	-3	-27,079,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	513	510	-3
Full-time equivalent of all other positions	50	50	--
Average number of all employees	562	555	-7
Personnel compensation:			
Permanent positions	$ 9,243,000	$ 9,343,000	+$100,000
Positions other than permanent	1,183,000	1,190,000	+7,000
Other personnel compensation	259,000	279,000	+20,000
Subtotal, personnel compensation	10,685,000	10,812,000	+127,000
Personnel benefits	1,542,000	1,574,000	+32,000
Travel and transportation of persons	415,000	386,000	-29,000
Transportation of things	50,000	45,000	-5,000
Rent, communications and utilities	430,000	420,000	-10,000
Printing and reproduction	250,000	236,000	-14,000
Other services:			
Project contracts	10,060,000	9,329,000	-731,000
Payment to NIH Management Fund	7,476,000	7,612,000	+136,000
Other	4,583,000	3,915,000	-668,000
Supplies and materials	1,990,000	1,686,000	-304,000
Equipment	2,660,000	1,750,000	-910,000
Grants, subsidies and contributions	101,893,000	77,190,000	-24,703,000
Total obligations by object	142,034,000	114,955,000	-27,079,000

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1975 House Report	
1. The Committee suggested that special emphasis be given to spinal cord regeneration (page 32).	1. The Director, NINCDS, established an Advisory Council Ad Hoc Subcommittee on Growth and Regeneration in the central nervous system in October 1973. Within the next year, four workshops were held dealing with major aspects of the problem. Also, a number of scientific papers were written on special aspects. The Subcommittee presented an outstanding report of the current status of research to the NANCDS council at its meeting in March 1975. This report will provide valuable guidance to future direction of research in this field.
2. The Committee hopes that the new computerized X-ray scanning equipment which is becoming more widely available will permit detection and treatment of abnormalities of the vascular system of the brain before strokes occur and will aid in the management of patients after a stroke (page 32).	2. These scanners are being applied to stroke and other head injury problems in several of the NINCDS clinical Research Centers. New methods of therapy are being developed and evaluated which ameliorate abnormalities before a stroke or aid in treatment after a stroke occurs.
3. The Committee wishes to encourage experienced research on electrodes for auditory prosthesis for implantation in totally deaf persons (page 32).	3. At the request of the Secretary of the Department of Health, Education, and Welfare, the NINCDS organized two workshops on the cochlear implants, one at Bethesda and one more recently in San Francisco to discuss the current status of an implantable cochlear auditory prosthesis. Although recognizing the formidable obstacles inherent in such devices, the conferees recommended research on the many problems in this area, and both grant and contract proposals are now being sought.
4. At next year's hearings the Committee will expect to hear a further report particularly on the implementation of the feasibility stage of the comprehensive epilepsy program (page 33).	4. With the feasibility stage nearly complete, the Institute is now planning to establish one or more comprehensive research and treatment center programs for epilepsy and related convulsive disorders. These programs will stress a comprehensive approach to the research and management of epilepsy.

Item	Action taken or to be taken
1975 House Report (cont'd)	
5. The Committee hopes that a significant increase in the level of research on multiple sclerosis will be conducted in 1975 (page 33).	5. The Institute is conducting and supporting approximately 41 research projects related to MS in an attempt to discover the cause of multiple sclerosis. One-half of these projects are in biochemistry and neurochemistry, and the others relate to immunology, neurophysiology, pathology, virology, and clinical studies.
6. The Committee understands that relatively little research is being done with autistic children and believes that a greater effort should be made to find the key to this tragic affliction (page 33).	6. Meetings have been held with members of the national voluntary agency interested in autism and a joint decision reached to organize a scientific workshop on the neurobiological aspects of the problem in order to form a basis on which improved clinical treatment can be developed. Planning of the workshop is in progress.
1975 Senate Report	
1. The Committee urges the NINCDS to further develop the new computerized X-ray scanning equipment to improve the management of the patient in the acute phase of stroke (page 52).	1. These scanners are being applied to stroke and other head injury problems in several of the NINCDS Clinical Research Centers. New methods of therapy are being developed and evaluated which ameliorate abnormalities before a stroke or aid in treatment after a stroke occurs.
2. The Committee expects an increased effort in research on Spinal Cord and Head Injury (page 52).	2. A recently launched national cooperative study is attempting to provide means of distinguishing those patients who could recover from injuries where the damage is reversible, from those who have permanently damaged brains. Other studies are being supported to improve methods of dealing with brain swelling, the most common cause of coma following head injury. The Director, NINCDS, established an Advisory Council Ad Hoc Subcommittee on Growth and Regeneration in the central nervous system in October 1973. With the next year, four workshops were held dealing with major aspects of the problem. Also, a number of scientific papers were written on special aspects. The Subcommittee presented an outstanding report of the current status of research to the NANCDS council at

Item	Action taken or to be taken
1975 Senate Report (cont'd)	
	its meeting in March 1975. This report will provide valuable guidance to future direction of research in this field.
3. In the field of multiple sclerosis the Committee hopes that the recommendations of the National Advisory Commission will be implemented (page 53).	3. The recommendations in the Commission's report submitted in February 1974 to the Secretary of HEW and to the Congress have been under careful study. The Institute has concurred in the recommendation and has implemented a number of recommendations, such as expansion of virological, immunological, and epidemiological research, and the funding of additional research centers.
4. The Committee wishes to encourage research on an auditory prosthesis which would aid the totally deaf (page 53).	4. At the request of the Secretary of the Department of Health, Education, and Welfare, the NINCDS organized two workshops on the cochlear implants, one at Bethesda and one more recently in San Francisco to discuss the current status of an implantable cochlear auditory prosthesis. Although recognizing the formidable obstacles inherent in such devices, the conferees recommended research on the many problems in this area, and both grant and contract proposals are now being sought.
5. The Committee expects a plan of study and means of implementation to be developed concerning research with autistic children (page 52).	5. Meetings have been held with members of the national voluntary agency interested in autism and a joint decision reached to organize a scientific workshop on the neurobiological aspects of the problem in order to form a basis on which improved clinical treatment can be developed. Planning of the workshop is in progress.
6. (F.Y. 1974 Report--page 49) The Committee also believes that this would be an opportune time for an "independent, unbiased" study of the fundamentals of the chiropractic profession.	6. In order to provide a substantive scientific base to conduct this study, the NINCDS convened a "Workshop on the Research Status of Spinal Manipulative Therapy," which was at NIH on February 2, 3 and 4, 1975. Nearly 60 participants from the fields of Medicine, Osteopathy, Chiropractic and Basic Science came from the United States and eight foreign countries. Proceedings including the papers presented and summaries of resultant discussions are in the process of publication.

Authorizing Legislation

Legislation	1976 Authorization	1976 Appropriation Requested
Public Health Service Act Section 301--Research and Investigations in general	Indefinite	
Title IV, Part D--National Institute of Neurological Diseases and Blindness	Indefinite	$107,055,000 2/
Public Law 90-639, Sec. 7--National Institute of Neurological Diseases and Stroke	Indefinite	
Title IV, Part I--National Research Service Award Act	1/	$ 7,900,000 2/

1/ Authorization expires June 30, 1975; extension legislation is proposed.

2/ Funding estimate only.

National Institute of Neurological and Communicative Disorders and Stroke

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$ 91,184,000	$ 91,184,000	$ 96,291,000	$ 95,841,000
1967	100,171,000	105,008,000	110,008,000	110,008,000
1968	120,285,000	120,285,000	125,310,000	120,269,000
1969	123,765,000	119,244,000	125,244,000	121,504,500
1970 1/	97,667,000	95,438,000	106,187,000	101,547,000
1971	89,475,000	95,073,000	110,073,000	100,073,000
1972	91,015,000	103,454,000	133,454,000	111,445,000
1973	111,394,000	122,405,000	129,735,000	124,005,000 2/
1974	100,769,000	119,644,000	124,571,000	119,529,000 3/
1975	119,494,000	131,496,000 4/	143,536,000	142,034,000
1976	114,955,000			

1/ $21,519,000 transferred to National Eye Institute
2/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.
3/ Appropriation after reduction.
4/ Excludes contracts not considered by House due to lacking authorization.

National Institute of Neurological and Communicative Disorders and Stroke

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$ 96,403,000	$ 96,403,000	$102,153,000	$101,153,000
1967	106,418,000	111,296,000	116,296,000	116,296,000
1968	128,633,000	128,633,000	136,633,000	128,633,000
1969	131,195,000	126,674,000	132,674,000	128,934,500
1970 1/	103,485,000	101,256,000	112,700,000	107,365,000
1971	96,972,000	100,807,000	115,807,000	103,502,000
1972	96,521,000	108,590,000	139,187,000	116,731,000
1973	117,877,000	130,673,000	145,000,000	130,672,000 2/
1974	101,198,000	120,073,000	125,000,000	121,358,000 3/
1975	119,958,000	131,960,000 4/	144,000,000	142,498,000
1976	114,955,000			

1/ Excludes funds for blindness, established as a separate appropriation "National Eye Institute" in 1970.
2/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.
3/ Appropriation after reduction.
4/ Excludes contracts not considered by House due to lacking authorization.

Justification

National Institute of Neurological and Communicative Disorders and Stroke

Authorizing Legislation: Public Health Service Act, Public Law 410, Title IV, Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	513	$ 12,227,000	510	$ 12,386,000	-3	+$159,000
Other expenses.....	--	129,807,000	--	102,569,000	--	-27,238,000
Total.....	513	142,034,000	510	114,955,000	-3	-27,079,000

General Statement

Research funded by the National Institute of Neurological and Communicative Disorders and Stroke is intented to provide an increased understanding of the brain, spinal cord, and related nervous and sensory systems and the many disorders which afflict them. Many of these disorders interfere with mobility and often cause long-term disability such as that which occurs in cerebral palsy, multiple sclerosis, muscular dystrophy and parkinsonism. Some interfere with education and employment such as epilepsy, deafness, and speech disorders. And stroke, the third leading cause of death in this country, and head and spinal cord trauma are major causes of serious disability.

These neurological and communicative disorders fall into 4 major program areas, within each of which are specifically focused research efforts. These research efforts are carried out through extramural project research grants, center or program project research grants, intramural research projects, collaborative and field research projects and contract research projects. The various focused efforts are the following:

The neurological disorders of early life, including cerebral palsy and such metabolic diseases as Tay-Sachs.

The neurological disorders of adult life including Parkinson's disease and Huntington's disease.

The cerebrovascular disorders, particularly stroke.

Epilepsy and related paroxysmal disorders including migraine headaches.

Multiple sclerosis and related disorders.

Neuromuscular disorders, particularly muscular dystrophy and myasthenia gravis.

Infectious diseases of the nervous system, including those chronic degenerative diseases caused by slow and latent viruses.

Spinal cord and head injury, and central regeneration.

Tumors of the nervous system.

Neuroendocrine studies, including studies on the autonomic nervous system, and on control of body temperature, bladder, and respiration.

Neural aspects of learning and behavior, such as sensory and motor behavior, perception, memory, learning, and locomotion.

Normal nervous system functions, including the subcategories of anatomy, biochemistry, pharmacology and physiology.

Communicative disorders including disorders of hearing and equilibrium, speech and language, and other higher brain functions, and disorders of other senses.

National Institute of Neurological and Communicative Disorders and Stroke

Budget Mechanism

	1975 Estimate*			1976 Estimate		
	Number	FTE 1/	Amount	Number	FTE 1/	Amount
Grants						
Regular						
Non-competing	676	--	$49,107,000	650	--	$ 49,017,000
Competing	190	--	14,459,000	104	--	8,593,000
New	355	--	16,077,000	60	--	2,740,000
Supplemental	(65)	--	1,100,000	(70)	--	1,150,000
Subtotal	1,221	--	80,743,000	814	--	61,500,000
Special						
Specialized Research Centers	--	--	5,891,000	--	--	5,691,000
Scientific Evaluation	--	--	205,000	--	--	236,000
Research Career Program	93	93	2,031,000	87	87	1,863,000
Subtotal	93	93	8,127,000	87	87	7,790,000
Total Grants	1,314	93	88,870,000	901	87	69,290,000
Fellowships						
Non-competing	24	24	529,000	190	218	3,200,000
Competing	--	--	--	--	--	--
New	170	198	2,912,000	63	74	900,000
Supplemental	--	--	--	--	--	--
Subtotal	194	222	3,441,000	253	292	4,100,000
Training Grants						
Non-competing	162	527	9,582,000	50	170	3,800,000
Competing	--	--	---	--	--	--
New	--	--	---	--	--	--
Supplemental	--	--	--	--	--	--
Subtotal	162	527	9,582,000	50	170	3,800,000
Laboratory & Clinical Research			18,815,000			17,594,000
Research and Development Contracts			10,060,000			9,329,000
Collaborative Research and Support			6,962,000			6,412,000
Research Management and Program Services			4,304,000			4,430,000
Total			142,034,000			114,955,000

*Excludes 1973 appropriation restoration

1/ Full-time equivalents

DHEW - National Institutes of Health

CROSSWALK - 1975 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute of Neurological and Communicative Disorders and Stroke
(Dollars in thousands)

Program \ Mechanism	Research Grants				Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials							
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Communicative Disorders	6,823	4,840	89	214	2,884	657		1,333		16,840
2. Neurological Disorders	24,671	19,183	2,625	1,810	5,573	2,472		6,354		62,688
3. Stroke and Nervous System Trauma	9,252	2,681	2,803	71	802	--		1,787		17,396
4. Fundamental Neurosciences	8,361	4,932	374	141	323	312		586		15,029
5. Intramural Lab. and Clinical Research							18,815		6,962	25,777
6. Research Man. and Program Services									4,304	4,304
Total obligations	49,107	31,636	5,891	2,236	9,582	3,441	18,815	10,060	11,266	142,034

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute of Neurological and Communicative Disorders and Stroke
(Dollars in thousands)

Mechanism / Program	Research Grants						Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials		Training Programs					
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Communicative Disorders	9,209	1,759	89	250	1,053	777		1,181		14,318
2. Neurological Disorders	24,958	7,049	2,433	1,620	2,207	1,888		5,905		47,060
3. Stroke and Nervous System Trauma	7,600	1,542	2,795	97	400	82		1,787		14,303
4. Fundamental Neurosciences	7,250	2,133	374	132	140	353		456		10,838
5. Intramural Lab. and Clinical Research							17,594		6,412	24,006
6. Research Man. and Program Services									4,430	4,430
Total obligations...	49,017	12,483	5,691	2,099	3,800	4,100	17,594	9,329	10,842	114,955

Communicative Disorders

Authorizing Legislation: Public Health Service Act, Public Law 410, Title IV, Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	--	---	--	---	--	---
Other expenses	--	$16,840,000	--	$14,318,000	--	-$2,522,000
Total	--	16,840,000	--	14,318,000	--	-2,522,000
Subactivities:						
Hearing and equilibrium	--	10,493,000	--	9,389,000	--	-1,104,000
Speech and language	--	2,592,000	--	2,849,000	--	+257,000
Research career programs	--	214,000	--	250,000	--	+36,000
Research training programs	--	3,541,000	--	1,830,000	--	-1,711,000
Total	--	16,840,000	--	14,318,000	--	-2,522,000
Funding mechanism:						
Research Grants						
Regular	--	11,663,000	--	10,968,000	--	-695,000
Special	--	303,000	--	339,000	--	+36,000
Subtotal	--	11,966,000	--	11,307,000	--	-659,000
Fellowships	--	657,000	--	777,000	--	+120,000
Training grants	--	2,884,000	--	1,053,000	--	-1,831,000
Research and development contracts	--	1,333,000	--	1,181,000	--	-152,000
Total	--	16,840,000	--	14,318,000	--	-2,522,000

The Communicative Disorders program of the National Institute of Neurological and Communicative Disorders and Stroke is concerned with research on improving the diagnosis, treatment, and prevention of diseases and disorders which affect the ear, nose and throat and cause problems relating to hearing, language, and speech. More than 20 million Americans are afflicted with hearing, speech and language problems. Included in this figure are an estimated 14 million persons with a handicapping communication impairment, of whom some 2 million are significantly or profoundly deaf; approximately 2 million persons have an impaired ability to comprehend language; and about 10 million persons have speech disorders. These figures--swollen by the large number of children crippled with multiple communicative disorders born during the 1963-64 rubella epidemic--reflect the enormous scope of the problem.

The communication process may be impaired by a multitude of problems including poor amplification of the message or interference with interpreting the incoming messages, storing and processing the information, or generating meaningful language. Physical speech disorders may result from problems with any of the structures producing speech, such as the larynx, palate and mouth. Problems also can originate from emotional problems, poor muscle coordination, deafness or language disorders.

Through clinical research centers, program projects, and individual grants, and at the newly created laboratory of neuro-otolaryngology in Bethesda, the NINCDS is studying the prevention of communication disorders through an understanding of the biological functions involved, and supporting clinical studies on improved treatment.

Special emphasis is being given to research on secretory (serous) otitis media (a painless chronic middle ear affliction that is a major cause of hearing loss in children), on ototoxic agents which damage the ear, on disturbances of the vestibular (balance) system, on speech and language problems, on the early detection and treatment of diseases of the larynx, and on noise. The possibility is being examined of stimulating the nerve endings in the inner ear through the so-called cochlear implant, since experimentally, some degree of auditory sensation has been provided for the profoundly deaf.

In addition, major contract-supported research encompasses several projects which include: experimental utilization and evaluation of a recently developed master hearing aid; development of better speech analyzing aids or cues for the deaf; examination of the question of a critical age for language learning by children; and studies of noise as it affects hearing and speech--a project (together with those of the National Institute of Environmental Health Sciences) included in the Federal effort on control of noise pollution coordinated by the Environmental Protection Agency.

Objectives, 1976: In 1976, The Institute will continue research towards the diagnosis, treatment and prevention of disorders and diseases of the ear, nose and throat, and of human communication.

Neurological Disorders

Authorizing Legislation: Public Health Service Act, Public Law 410, Title IV, Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	--	---	--	---	--	---
Other expenses	--	$62,688,000	--	$47,060,000	--	-$15,628,000
Total	--	62,688,000	--	47,060,000	--	-15,628,000
Subactivities:						
Neurological disorders of early life	--	12,490,000	--	9,942,000	--	-2,548,000
Neurological disorders of adult life	--	3,612,000	--	2,997,000	--	-615,000
Epilepsy	--	5,776,000	--	4,109,000	--	-1,667,000
Sclerosing disorders	--	6,230,000	--	4,839,000	--	-1,391,000
Neuromuscular disorders	--	7,284,000	--	5,705,000	--	-1,579,000
Infectious diseases of the central nervous system	--	2,445,000	--	2,002,000	--	-443,000
Tumors of the nervous system	--	1,111,000	--	753,000	--	-358,000
Neuroendocrine studies	--	3,794,000	--	2,793,000	--	-1,001,000
Learning and behavior	--	2,417,000	--	1,908,000	--	-509,000
Other sensory disorders	--	7,879,000	--	5,533,000	--	-2,346,000
Research career programs	--	1,605,000	--	1,384,000	--	-221,000
Research training	--	8,045,000	--	5,095,000	--	-2,950,000
Total	--	62,688,000	--	47,060,000	--	-15,628,000
Budget mechanism:						
Research Grants:						
Regular	--	43,854,000	--	32,007,000	--	-11,847,000
Special	--	4,435,000	--	4,053,000	--	-382,000
Subtotal	--	48,289,000	--	36,060,000	--	-12,229,000
Fellowships	--	2,472,000	--	2,888,000	--	+416,000
Training grants	--	5,573,000	--	2,207,000	--	-3,366,000
Research and development contracts	--	6,354,000	--	5,905,000	--	-449,000
Total	--	62,688,000	--	47,060,000	--	-15,628,000

Of the four major research program segments, Neurological Disorders contains the largest grouping of subprograms. These neurological disorders fall into ten separate areas, each the subject of a specifically focused research effort directed at advancing knowledge of the human nervous system and how it functions in health and disease.

Objectives 1976: Research emphasis in 1976 will be focused on epilepsy, including the establishment of one or more comprehensive epilepsy research center programs; multiple sclerosis; genetic and developmental disorders; further analysis and publication of data collected from the collaborative perinatal project; and on virological and immunological aspects of chronic degenerative diseases of the nervous system.

Significant research being conducted in some of the program areas include the following:

a. Neurological Disorders of Early Life. This category includes the Collaborative Perinatal Project. This program is nearing completion after a long-term followup at seven and at eight years of age on children born to 50,000 women at 12 collaborating major medical centers.

The basic objective of the program has been to relate complications, conditions, and events that occur during a woman's pregnancy or during labor and delivery, to subsequent nervous system abnormalities exhibited by the child of the pregnancy.

As data collection ends, the major emphasis of the program has shifted to data analysis and the publication of reports on the Project's research findings.

The analyses include 10 primary areas: cerebral palsy and motor disorders; mental retardation; vision abnormalities; convulsive disorders; learning disorders and minimal brain dysfunction; communicative disorders (problems of speech, language, and hearing); congenital malformations; multiple problems associated with low birth-weight and gestational age (prematurity); and the children who died during the interval of the Study, with particular emphasis on the abnormalities found in the central nervous system.

b. Epilepsy. In 1975 and 1976, the Institute will establish one or more comprehensive research and treatment center programs for epilepsy and related convulsive disorders. These programs will stress a comprehensive approach to applied and fundamental research, and will be strongly oriented toward the development of new and improved methods of diagnosis, treatment, and rehabilitation regardless of age or severity. The primary emphasis will be on the application of new research findings to patients. The ultimate goals of these programs will be the development of new antiepileptic drugs in the search for complete control of seizures, the reduction of the debilitating side effects of presently available epileptic drugs, and restoration of patients with controlled seizures to a useful and productive life.

c. Multiple Sclerosis. In multiple sclerosis, a major event has been completion of work by the National Advisory Commission on Multiple Sclerosis. The recommendations in the Commission's report submitted in February 1974 to the Secretary of HEW and to the Congress have been concurred in by the Institute and an expanded research effort in multiple sclerosis has been implemented, notably in virological, immunological, and epidemiological research, and the creation of two additional research centers.

The Institute is conducting and supporting approximately 41 research projects related to MS in an attempt to discover the cause of multiple sclerosis. One-half of these projects are in biochemistry and neurochemistry, and the others relate to immunology, neurophysiology, pathology, virology, and clinical studies. Chemical and metabolic characteristics of normal and abnormal myelin have been extensively investigated in an attempt to reach an understanding of how myelin is formed maintained and degraded in the normal nervous system. The search for a viral agent is closely related to this approach, since many investigators believe that an autoimmune process may be triggered by a virus in the causation of multiple sclerosis.

Three multidisciplinary NINCDS-supported clinical programs are conducting studies on patients, involving immunological, virological, and neurochemical aspects relevant to demyelinating disease.

d. Muscular Dystrophy, Myasthenia Gravis, and other Neuromuscular Diseases. Research in this group of diseases is centered in about 130 research projects in numerous hospitals, medical schools, and universities, including two program project grants, and in the medical neurology branch in the Institute's intramural program. The treatment for myasthenia gravis recently introduced by Institute scientists and involving high single-dose alternate-day prednisone has been established as the treatment of choice in many patients. Special interests and opportunities are: tissue culture studies of differentiating muscle cells aimed at elucidating the nature of intrinsic muscle disorders like muscular dystrophy; immunochemical studies utilizing antibodies against pure nerve-to-muscle receptor proteins--studies which provide animal models closely resembling human myasthenia gravis; the use by NINDS scientists of freeze-fracture electron microscopy to obtain a panoramic, birds-eye-view of cell membrane surfaces--a technique which has provided for the first time visualization of distinctive structural differences between nerve-to-nerve junctions that are excitatory and those that are inhibitory; and the fabrication of special electrodes that allow experimental recording of nerve and muscle electrical activity during free movement. This last achievement is a real breakthrough by NINDS scientists that permits the study of active muscles, in contrast to previous conventional techniques which are suitable only for muscles at rest.

e. Infectious Diseases of the Central Nervous System. The Institute's program in slow and atypical viruses as described in the section on Laboratory and Clinical Research is a major research undertaking. In addition, the Institute has a highly significant program carried on by its grant and contract programs and its Intramural Research component in relation to the Collaborative Perinatal Research project. This latter program is concerned with the study of the relationship between viral, bacterial, mycoplasma and protozoal infections in the perinatal period, and resultant birth defects and pediatric neurological diseases. Recent advances have been made in studies of the effects of herpes virus infections, toxoplasmosis, cytomegalovirus infections, and rubella vaccine during pregnancy. The role of measles virus in the causation of subacute sclerosing panencephalitis, a fatal disease in children, has been clarified. Studies are also in progress on the relationship of myxovirus-like viruses in the etiology of multiple sclerosis.

f. Brain tumors. Brain tumors comprise a group of several histologically and biologically different tumors. Brain tumors of childhood represent 26% of childhood cancers, but are quite different from the brain tumors of adults which constitute only about 7% of adult cancer. Nearly one-half of the people who die of neurological disease other than stroke die of brain tumors.

Surgical removal of the encapsulated well-differentiated slow-growing tumors can effect a cure, and the development of microsurgical techniques is increasing the number of surgical cures. Patients with malignant brain tumors

(the glioblastoma multiforme, which constitutes about 45% of adult brain tumors) have a median survival of about 5 months. Recent work in the Branch of Surgical Neurology has shown that when combined oral and intratumoral chemotherapy are added to conventional therapy, surgery and X-Ray, the mean survival time is doubled when compared to controls receiving conventional treatment only. In addition it has been shown that the cellular immune mechanisms of patients with low grade gliomas (benign course) are the same as in patients without tumors and cancer, but the high grade glioma patients (malignant course) display decreased cellular immune responses.

Stroke and Central Nervous System Trauma

Authorizing Legislation: Public Health Service Act, Public Law 410, Title IV, Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	--	---	--	---	--	---
Other expenses.....	--	$17,396,000	--	$14,303,000	--	-$3,093,000
Total.....	--	17,396,000	--	14,303,000	--	-3,093,000
Subactivities:						
Stroke.....	--	9,027,000	--	7,720,000	--	-1,307,000
Trauma and injury.....	--	7,496,000	--	6,004,000	--	-1,492,000
Research career programs.....	--	71,000	--	97,000	--	+26,000
Research training.....	--	802,000	--	482,000	--	-320,000
Total.....	--	17,396,000	--	14,303,000	--	-3,093,000
Budget mechanism:						
Research Grants						
Regular.....	--	11,933,000	--	9,142,000	--	-2,791,000
Special.....	--	2,874,000	--	2,892,000	--	+18,000
Subtotal.....	--	14,807,000	--	12,034,000	--	-2,773,000
Fellowships.....	--	---	--	82,000	--	+82,000
Training grants.....	--	802,000	--	400,000	--	-402,000
Research and development contracts....	--	1,787,000	--	1,787,000	--	---
Total.....	--	17,396,000	--	14,303,000	--	-3,093,000

The funds requested for 1976 will be used for research programs on stroke, directed towards the main problems of prevention, diagnosis, acute care, and long term consequences. In the fields of spinal cord injury and regeneration, plans include the evaluation of recent leads in central nervous system regeneration.

Within the program area of Stroke and Central Nervous System Trauma there are four major scientific efforts; these are in the areas of Stroke, Head Injury, Spinal Cord Injury and Nervous System Regeneration.

Stroke. Stroke is the third leading cause of death in the United States and one of the leading causes of disability. The annual death rate is approximately 200,000; moreover, the 300,000 persons who survive strokes each year often suffer lifelong physical and mental incapacity. The Institute's research program in this area includes a coordinated effort of investigator-

initiated research, contract research and a program of stroke clinical research centers, 15 of which are active currently, and stroke acute care research units, with 11 now in operation.

One primary objective of stroke research is the protection of the brain during the acute phase of a cerebrovascular accident in order to assure the viability and continued function of brain cells. New non-invasive procedures are being developed to diagnose and monitor such problems. Of particular promise are new scanning instruments utilizing x-rays combined with computers to detect difference in nerve tissue density which reflect excess fluid (edema) and loss of blood (ischemia). These scanners are being applied to stroke and other head injury problems in several of the NINDS Clinical Research Centers. New methods of therapy are being developed and evaluated which may protect the patient's brain just prior to an impending stroke or during its acute phases. The Institute's Stroke Acute Care Research Unit Programs are focused on developing these methods of immediate intervention.

Because of the increased evidence that anti-hypertensive therapy is effective in preventing stroke, there is continued research being conducted on the cause of hypertension. The role of a specialized area of the brain, the hypothalamus, is being evaluated in the primary cause of essential hypertension, the principal type of high blood pressure.

Head Injury. The investigation of improved methods of diagnosis and treatment of head injury is a high priority research area of the NINDS. This research is both basic and clinical. In the clinical area, the Institute supports five clinical research centers. These clinical research groups direct their attention to the problems of brain swelling after injury, the physiological and metabolic consequences of head injury, the physical forces involved in brain damage, the structure and function of the blood-brain barrier, and the evaluation of new diagnostic and therapeutic procedures in the management of head injury.

A fundamental question regarding brain injury is whether patients who are admitted to the hospital in coma with signs of brain damage have sustained an irreversible injury at the moment of impact or shortly thereafter, or whether they are comatose because of complications of the injury which may be reversible. A recently launched national cooperative study is attempting to provide means of distinguishing those patients who could recover from injuries where the damage is reversible, from those who have permanently damaged brains. In conjunction with this, studies are being supported to improve the therapeutic methods of dealing with brain swelling, the most common cause of coma following head injury.

Spinal Cord Injury and Regeneration. The incidence of spinal cord injury as a result of both traffic and recreational accidents continues to increase. These injuries, often resulting in paraplegia, have serious consequences for the victim, his family, and the community. A Subcommittee of the NANCDS Council has been examining the current status of central nervous system regeneration with special reference to spinal cord injuries, in order to identify promising research leads.

More information is needed on the immediate damage in the injured spinal cord. Preliminary data suggest that if the acute injury is properly treated immediately, permanent damage may be prevented. Increasing efforts also are needed to develop prostheses that can utilize still viable muscles even though long tracts of the spinal cord have been damaged. This is an area where the multidisciplinary approach of neurological scientists, biophysicists, and engineers is essential.

Fundamental Neurosciences

Authorizing Legislation: Public Health Service Act, Public Law 410 Title IV, Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	--	---	--	---	--	---
Other expenses.....	--	$15,029,000	--	$10,838,000	--	-$4,191,000
Total.....	--	15,029,000	--	10,838,000	--	-4,191,000
Subactivities:						
Nervous System Studies related to normal function.....	--	7,394,000	--	4,570,000	--	-2,824,000
Multicategorical.....	--	6,859,000	--	5,643,000	--	-1,216,000
Research career program	--	141,000	--	132,000	--	-9,000
Research training.....	--	635,000	--	493,000	--	-142,000
Total.....	--	15,029,000	--	10,838,000	--	-4,191,000
Budget mechanism:						
Research Grants:						
Regular.....	--	13,293,000	--	9,383,000	--	-3,910,000
Special.....	--	515,000	--	506,000	--	-9,000
Subtotal.....	--	13,808,000	--	9,889,000	--	-3,919,000
Fellowships.....	--	312,000	--	353,000	--	+41,000
Training grants.....	--	323,000	--	140,000	--	-183,000
Research and development contracts.....	--	586,000	--	456,000	--	-130,000
Total.....	--	15,029,000	--	10,838,000	--	-4,191,000

This program area encompasses those fundamental or basic research projects that are not readily identified with the communicative disorders, neurological disorders, or stroke and trauma programs.

In 1976, funds for extramural research in the Fundamental Neurosciences will support a variety of types of projects, including research grants, training grants, and fellowships. The projects supported will be a carefully selected balance of ongoing projects as well as the initiation of new ones.

The diseases of the human nervous sytem are among the most chronic, debilitating, costly, and least understood of all those that afflict man. Support in the fundamental neurosciences represents the investment by NINCDS in the problem areas and at the frontiers of research on how the normal functioning of the nervous system is altered in the various neurological diseases.

Because of the complexity of the human nervous system, the investment comprises a vast collaborative effort of clinicians and neuroscientists for whom these problem areas and frontiers represent some of the most challenging and perplexing that confront any group of biomedical investigators.

The human nervous system, unlike other bodily organs cannot be replaced or substituted. Unlike all other cells in the body, the principal cell of the nervous system, the neuron, cannot reproduce itself. At birth persons possess their fixed complement of neurons. Any losses are irreplaceable; the original allotment must last a lifetime.

The functional principle of the nervous system is of a chemically-mediated communications system. From the brain and spinal cord the nervous system impinges upon every part of the body to initiate or regulate virtually all bodily activities and to receive back and respond to information on the status of these activities.

Hence the neuroscientist faces a variety of formidable difficulties in attempting to elucidate the mechanism responsible for normal functioning and to understand the nature of its derangements. Few of the fundamental studies can be done directly on the human central nervous system. The use of other species and the development of highly sophisticated specialized techniques are often the rule rather than the exception. Hence, most of the fundamental knowledge about the mechanisms by which a nerve conducts impulses have derived from studies on the giant axon (nerve) of the squid and required the development of the voltage-clamp and other techniques which have provided the major biological tools for electrophysiological studies on the nervous system, contributions made in large measure by NINCDS intramural scientists.

Many other areas of important basic research could be described. A nerve growth factor has been discovered which in extremely low concentrations causes a remarkable growth in nerve fibers. Many efforts are being made to modify the shape or chemical composition of drug and chemical molecules in subtle ways to try to make them more effective in therapy, to reduce their toxicity, and to develop chemical tools to elucidate cellular functions and structures. Examples are new and better anesthetics, drugs for the treatment of epilepsy and parkinsonism, and chemicals for analytical tools to study nerve membrane structure and other neurophysiological problems. These important approaches involve such sophisticated techniques as x-ray crystallography, electron paramagnetic resonance spectroscopy, and nuclear magnetic resonance spectroscopy. On the basis of such highly specialized information on the atomic relationships and the electron activity in the effective molecules, it will be possible to synthesize other compounds that are more effective or which play a crucial role in studies on how present drugs work.

The foregoing glimpse of the nature and significance of the NINCDS investment in the neurosciences is necessarily incomplete. In fact, neurosciences must be considered a continuum from the realm of human behavior and the patient's bedside to the most fundamental question of the biology of a slow virus or the molecular nature of a membrane receptor. The most elementary problem of neurology, the conduction of nerve impulses, seem to be slowly yielding under the applications of increasingly powerful concepts and techniques. On the other hand the neuroscientist is the constant collaborator of the clinical neurologist because the ultimate solutions and the ultimate challenges are in the human central nervous system.

Intramural Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act, Public Law 410, Title IV, Part D

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	421	$10,291,000	418	$10,413,000	-3	+$122,000
Other expenses.....	--	15,486,000	--	13,593,000	--	-1,893,000
Total.....	421	25,777,000	418	24,006,000	-3	-1,771,000
Budget mechanism:						
Laboratory and clinical research...	285	18,815,000	284	17,594,000	-1	-1,221,000
Collaborative research and support..	136	6,962,000	134	6,412,000	-2	-550,000
Total.....	421	25,777,000	418	24,006,000	-3	-1,771,000

The Intramural Research Program of the National Institute of Neurological Diseases and Stroke conducts research related to the nervous system and its disorders in its laboratories and clinics in Bethesda, Maryland.

Clinical Research Program. The clinical units of the Intramural Program conduct research on a large number of neurological disorders which arise because of malfunction of the nervous system. The emphasis is to develop new knowledge from basic research and apply it to new and improved treatment or preventive measures.

In the medical neurology area, research will continue on motor neuron diseases, myopathies, dystrophies, and diseases of the neuromuscular junction. An increased emphasis will be placed on the immunological aspects of these diseases and other disorders that involve the central nervous system.

In the surgical neurology and electroencephalography areas, research is focused on stroke, the epilepsies, head injury, chemotherapy and immunotherapy of cerebral tumors, parkinsonism and other dyskinesias, and on new methods of diagnosis of the abnormal structure and function in the spinal cord and brain. Special attention is being given to experimental stroke models, to microsurgical therapeutic approaches, and to radiological monitoring. A computerized axial tomographic scanner is on order for experimental studies in these fields.

In the developmental and metabolic neurology areas, enzyme replacement therapy for the inherited disorders of lipid metabolism such as Fabry's, Tay-Sachs, Gaucher's, Niemann-Pick and other similar diseases continues to be evaluated. Increased capability is needed to produce adequate amounts of enzymes for treatment trials. Basic enzymology continues as an important aspect of the studies in order to determine in what way the enzymes are defective in afflicted individuals and to develop information necessary for correcting the enzyme defects.

During 1975 two new programs have been established: one in neuroimmunology which will be concerned with clinical problems of autoimmunity (like multiple sclerosis), with slow and latent virus diseases, and with coordination of immunological aspects of the many virological projects in various intramural laboratories; the other in neuropharmacology involving conduct of basic as well as clinically applied studies of central neurohumoral mechanisms and the relevant pathogenesis of disorders of motor, sensory, and behavioral function. A major goal is to develop improved pharmacologic therapies for neurologic disease, notably parkinsonism and Huntington's disease.

Laboratory Program. The laboratory research units of the Intramural Program conduct a broad array of research projects aimed at creating innovations that will form a basis for later developmental and applied work. The majority of these projects are investigator-initiated and are carried on within the laboratories and branches by individual scientists or groups, depending upon the type of research activity necessary. The justification for supporting investigator-initiated research comes from the recognition that progress depends on the creativity of an individual who makes important discoveries of broad applicability to medicine. There is no evidence that there is a more efficient way to generate important discoveries with a high impact on the prevention or treatment of disease than to encourage creative individuals or small groups to pursue ideas arising from their own knowledge and expertise. Although not always highly visible in the ultimate application of the discovery, the investigator-initiated research effort is the predominate if not the only mechanism to create new knowledge with which to achieve progress.

A strong thrust to gain new knowledge about the functions of individual nerve cells and nerve networks and their sensory and motor connections will continue. The basic mechanism of nerve excitation and how information is transferred by cells is still poorly understood. Also inadequate is our knowledge of this transfer mechanism for the neural elements in the brain, in the eye, and in the cochlea of the ear. Microspectrophotometry, neurophysiological and cytological studies on invertebrates and vertebrates, electrical recording from single cells, electronmicroscopy especially with freeze fracturing techniques are some of the important approaches used for data collection. One focus of effort will be the study of molecular reactions in nerve cell membranes that are specifically coupled to the excitation phenomena. Particular elucidation will be sought for the ions involved and the nature of the channels through which they flow. Also studied will be the enzyme composition of the membranes and how the enzymes function in relation to excitation or ionic or molecular transport.

Also emphasized are studies on motor control systems in the spinal cord or cerebral cortex, techniques for obtaining information transfer within the nervous system, feasibility of neural prosthesis for the sensory handicapped, and the applied technology of functional stimulation of nerve and muscle tissue. Information gained by research on chronic electrode tolerance by the central nervous system may make it possible, for example, to directly stimulate the visual auditory areas of brain as prosthetic approaches to blindness or deafness. A new effort to study the biologic mechanisms of hearing has begun. An increased understanding of the afferent and efferent neural auditory system is sought.

The necessity for understanding the biology of viruses has become increasingly evident. There is a continuing attempt to identify and characterize the viruses that cause some of the subacute presenile dementias as well as to determine whether other degenerative diseases of the nervous system are caused by transmissible agents. There is now good evidence that four human and two animal degenerative diseases of the brain can be attributed to transmissible

viruses. It is thus possible that other important diseases of the nervous system, such as amyotrophic lateral sclerosis or multiple sclerosis, could also be caused by viruses. It is expected that the effort to identify a transmissible viral cause of degenerative neurological disorders and other intramural research notably in immunology related to viruses will necessarily be expanded.

The evaluation of the basic reactions of the nervous system to injury and disease remains the prevailing theme of work. The elucidation of the pathological mechanism of cerebral stroke and the demyelinative mechanisms involved in multiple sclerosis are two important research areas. The permeability of the blood brain barrier, the study of cerebral ischemia and edema, and the structure of synaptic junction are also areas of considerable importance for the understanding of nervous system function. There is also the important question of how to initiate or control effective regeneration of axons after their destruction in the spinal cord or brain. Recent research findings indicate the desirability of further expansion of efforts to obtain new knowledge about nerve growth and regeneration.

There is an increasing need for the knowledge and techniques of molecular biology and biochemistry to be applied to the problems of the normally functioning or damaged nervous system. Since the ultimate understanding of nerve function will require a detailed knowledge of the molecular interaction within nerve cells, there are many and varied research approaches being pursued within these two research areas. The studies encompass the enzymological aspects of neural function, metabolism of neurohumoral transmitter substances, composition of cellular membranes, regulation of metabolism in gliomas, neuroblastoma and virally transformed cell lines, metabolism and synthesis of complex lipids, myelination of the nervous system, genetic regulation in human cells and regulation of viral nucleic acids among many others.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Public Law 410 Title IV, Part D

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	92	$1,936,000	92	$1,973,000	--	+$37,000
Other expenses.....	--	2,368,000	--	2,457,000	--	+89,000
Total.....	92	4,304,000	92	4,430,000	--	+126,000

Included in this activity is the administrative support required for the Extramural Programs and the Office of the Director. The Extramural Programs administers the Institute's grant and award programs in support of medical research and training in the neurological and communicative disorders. The Office of the Director provides the professional and administrative direction of the Institute's activities. Also included in this program are funds to support program evaluation as directed by DHEW and NIH.

Objectives 1976: The Institute will maintain the same level of administrative support as furnished in 1974 and 1975 with emphasis on program planning and the manpower reporting system within the Office of the Director.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Program Purpose and Accomplishments

Activity: Communicative Disorders (Speech and Hearing) [Public Health Service Act, Public Law 410, Title IV, Parts D and I]

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$16,840,000	Indefinite	--	$14,318,000

Purpose: The Communicative Disorders program of the National Institute of Neurological and Communicative Disorders and Stroke is concerned with research on improving the diagnosis, treatment, and prevention of diseases and disorders which affect the ear, and hearing, language and speech.

Explanation: The Institute's programs combine extramural research and training grants, intramural laboratory research, and contract-supported collaborative, clinical and applied research and are directed at improving understanding of the underlying functions involved in hearing, expressing ideas through speech, and in the central neural processing of language.

Accomplishments in 1975: In 1975, under this program 149 research grants, 27 fellowships, 41 training grants, and 13 contracts were awarded. The Institute's programs in 1975 were directed towards improving understanding of the underlying functions involved in hearing, expressing ideas through speech, and in the central neural (brain) processing of language. Also programs were directed at learning how specific diseases interfere with these functions and at applying this understanding to the diagnosis, treatment, and prevention of these disorders.

Objectives for 1976: The estimate for 1976 provides for 138 research grants, 44 fellowships, 14 training grants, and 12 research contracts. The Institute will continue to support clinical research in oto-rhinolaryngology, audiology, speech pathology and basic research in the communicative sciences and related fields through investigator-initiated research grant awards of the Extramural Programs. Ongoing basic research in neurosciences relating to communicative disorders will continue in existing intramural laboratories.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Program Purpose and Accomplishments

Activity: Neurological Disorders (Public Health Service Act, Public Law 410, Title IV, Parts D and I)

1975 Estimate		1976	1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$62,688,000	Indefinite	--	$47,060,000

Purpose: Of the four major research program segments, that concerned with neurological disorders contains the largest grouping of subprograms. These neurological diseases fall into ten separate areas, each subject of a specifically focused research effort and directed at significantly advancing knowledge of the human nervous system and of how it functions in health and disease.

Explanation: Research support is directed towards the neurological diseases of adulthood, epilepsy, tumors of the nervous system, neuromuscular disorders, sclerosing disorders, neurological diseases of childhood, neurological aspects of learning and behavior, infectious diseases of the nervous system, and other sensory disorders.

Accomplishments in 1975: In 1975, 874 research grants, 145 fellowships, 99 training grants, and 47 contracts were awarded. Research was directed towards all the neurological disorders with emphasis in the fields of epilepsy, sclerosing disorders, parkinsonism and infectious diseases of the central nervous system.

Objectives for 1976: The estimate for 1976 provides for 550 research grants, 183 fellowships,29 training grants and 43 contracts. Research emphasis in 1976 will be focused on: epilepsy including the establishment of one or more comprehensive programs centered on research and treatment of epilepsy, on multiple sclerosis; genetic and developmental disorders; on the further analysis of data collected from the collaborative perinatal project; and on virological and immunological aspects of infectious disorders.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Program Purpose and Accomplishments

Activity: Stroke, Nervous System Trauma (Public Health Service Act, Public Law 410, Title IV, Parts D and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$17,396,000	Indefinite	--	$14,303,000

Purpose: Research under this program is directed towards cerebrovascular disease and stroke, head injury, spinal cord injury, and nerve growth and regeneration.

Explanation: This program includes the support of stroke or head injury clinical research centers, acute spinal cord injury centers, stroke acute care research units and national trials of improved methods of prevention, diagnosis and therapy.

Accomplishments in 1975: In 1975, support was provided for 125 research grants, 16 training grants, and 16 contracts. Research was directed towards stroke, head injury, spinal cord injury, and nerve growth and regeneration.

Objectives for 1976: The estimate for 1976 provided for 100 research grants, 6 fellowships, 5 training grants, and 16 contracts. Research programs on stroke during 1976 will be directed towards the problems of prevention, diagnosis, and acute care and long-term care. In the fields of head injury, spinal cord injury and regeneration, plans include the exploitation of recent leads in central nervous system regeneration as well as the protection of the brain and spinal cord during the acute phase of the trauma.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Program Purpose and Accomplishments

Activity: Fundamental Neurosciences (Public Health Service Act, Public Law 410, Title IV, Parts D and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$15,029,000	Indefinite	--	$10,838,000

Purpose: Support of research in those areas of the fundamental neurosciences not identifiable with the other three NINDCS program areas is basic to the Institute's mission to elucidate the mechanisms responsible for normal functioning of the human nervous system and to understand the nature of its diseases and disorders.

Explanation: This program supports research grants in ongoing projects and new highly meritorious scientific projects, such as studies related to normal nervous system function including anatomy, biochemistry, physiology, and pharmacology.

Accomplishments in 1975: In 1975, 166 research grants, 22 fellowships, 6 training grants, and 5 contracts were awarded. Research was directed towards the mechanisms responsible for normal functioning of the human nervous system and to the understanding of the nature of its diseases and disorders.

Objectives in 1976: The estimate for 1976 provides for 113 research grants, 20 fellowships, 2 training grants, and 3 contracts. The amount requested is for continued support of research in the fundamental neurosciences. These funds will be used to support research grants in ongoing projects, and to start new highly meritorious scientific projects, such as studies related to normal nervous system function including anatomy, biochemistry, physiology, and pharmacology.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Program Purpose and Accomplishments

Activity: Intramural Laboratory and Clinical Research (Public Health Service Act, Public Law 410, Title IV, Part D)

1976 Estimate		1976	Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
421	$25,777,000	Indefinite	418	$24,006,000

Purpose: The intramural research activities of the Institute are directed toward a broad program to investigate the basic characteristics of the nervous system and its diseases.

Explanation: Supporting this program effort are five branches and ten laboratories. The following are in the Clinical Research area: Medical Neurology, Surgical Neurology, Developmental and Metabolic Neurology, Electroencephalography, and Neuroimmunology. Under the Laboratory Research area are: Biophysics, Neurochemistry, Neurophysiology, Molecular Biology, Experimental Neurology, Neural Control, Neuropathology and Neuroanatomical Sciences, Perinatal Physiology, Central Nervous System Studies, Neuro-otology, and Neuropharmacology.

Accomplishments in 1975: In 1975 the Institute established two new laboratories in immunology and pharmacology. The program for the Laboratory of Neuroimmunology is directed towards the application at both basic and clinical levels of the latest advances in cellular as well as systemic immunologic knowledge and techniques to a number of major neurological and communicative disorders. Current observations of the pathogenesis of such disorders as multiple sclerosis, congenital deafness as well as many frank virological infections clearly implicate disorders of cellular immune reactions as the probable underlying causative factors.

The program for the Laboratory of Neuropharmacology is directed towards basic as well as clinically applied studies of central neurohumoral mechanisms and their relation to the pathogenesis of disorders of motor, sensory and behavioral function. The major goal of the laboratory will be to develop improved pharmacologic therapies for neurologic disease, such as parkinsonism and Huntington's disease.

Objectives for 1976: In 1976 the Institute will continue basic and clinical research in neurological and communicative disorders including genetic disorders of the nervous system, parkinsonism, epilepsy, spinal cord injury and communicative disorders.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Program Purpose and Accomplishments

Activity: Research Management and Program Services (Public Health Service Act, Public Law 410, Title IV, Part D)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
92	$4,304,000	Indefinite	92	$4,430,000

Purpose: Included in this activity is the administrative support required for the Extramural Programs and the Office of the Director. The Extramural Program administers the Institute's grant and award programs in support of medical research and training in the neurological and communicative disorders.

Explanation: The Office of the Director provides the professional and administrative direction of the Institute's activities. Also included in this program are funds to support program evaluation.

Accomplishments in 1975: Management's expanding need for access to multiplex data and its comprehensive analysis to provide a firm base for program planning, evaluating and reporting, demands a fully automated information system capable of being adjusted to changing requirements. Such a system is to be established and will permit a more refined assessment of Institute support patterns and needs in research and research training in neurological and communicative disorders.

Objectives for 1976: The Institute will maintain the same level of administrative support as furnished in 1975 with emphasis on the refinement of the extramural reporting system and the manpower reporting system within the Office of the Director.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$114,955,000	$28,739,000
Total, obligations	$114,955,000	$28,739,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Communicative Disorders	--	$ 14,318,000	--	$ 3,637,000
Neurological Disorders	--	47,060,000	--	11,378,000
Stroke and Nervous System Trauma	--	14,303,000	--	3,461,000
Fundamental Neurosciences	--	10,838,000	--	2,796,000
Intramural Laboratory and Clinical Research	418	24,006,000	418	6,304,000
Research Management and Program Services	92	4,430,000	92	1,163,000
Total obligations	510	114,955,000	510	28,739,000

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the National Institute of Neurological and Communicative Disorders and Stroke consistent with the 1976 Estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	510	510
Full-time equivalent of all other positions	50	50
Average number of all employees	555	555
Personnel compensation:		
Permanent positions	$ 9,343,000	$ 2,561,000
Positions other than permanent	1,190,000	326,000
Other personnel compensation	279,000	77,000
Subtotal, personnel compensation	10,812,000	2,964,000
Personnel benefits: civilian	1,574,000	521,000
Travel and transportation of persons	386,000	95,000
Transportation of things	45,000	11,000
Rent, communications and utilities	420,000	105,000
Printing and reproduction	236,000	59,000
Other services:		
Project contracts	9,329,000	1,975,000
Payment to NIH Management Fund	7,612,000	1,904,000
Other	3,915,000	950,000
Supplies and materials	1,686,000	421,000
Equipment	1,750,000	437,000
Grants, subsidies and contributions	77,190,000	19,297,000
Total obligations by object	114,955,000	28,739,000

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. DORLAND J. DAVIS, DIRECTOR
DR. RONALD LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. JOHN R. SEAL, SCIENTIFIC DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
DR. ALFRED M. WEBB, CHIEF, PROGRAM PLANNING AND PROJECTION, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
CHARLES E. LEASURE, JR., EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
MARTIN J. FULLER, JR., FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We will continue with the National Institutes of Health. We now have the National Institute of Allergy and Infectious Diseases.

The presentation will be made by Dr. Dorland J. Davis, the Director. We have a biographical sketch of you, Doctor, which we will place in the record at this point.

[The biographical sketch follows:]

BIOGRAPHICAL SKETCH OF DORLAND J. DAVIS, M.D.

Position: Director, National Institute of Allergy and Infectious Diseases.

Birthplace and date: Chicago, Ill., July 2, 1911.

Education: B.S., University of Illinois, 1933; M.D., Johns Hopkins University, 1937; Dr. P.H. (epidemiology), Johns Hopkins University, 1940; and Certified by the American Board of Preventive Medicine and Public Health, 1949.

Experience: Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1964 to present; Associate Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1956–64; Chief, Laboratory of Infectious Diseases, National Microbiological Institute (now National Institute of Allergy and Infectious Diseases) NIH, 1954–56; and Commissioned Officer on duty at National Institutes of Health (1943–44 on duty in North Africa for the State Department), advanced through grades to Assistant Surgeon General (1968), 1939 to present.

Association memberships: Fellow, American Academy of Microbiology; Fellow, American College of Preventive Medicine; Fellow, American Academy of Allergy; American Association of Immunologists; American Epidemiological Society; American Society of Tropical Medicine and Hygiene; Board of Directors, Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc.; and member National Research Council, Division of Medical Sciences (Executive Committee, 1966–71).

Special awards, citations, or publications: Edward Rhodes Stitt Award, Association of Military Surgeons of the United States, 1955; Meritorious Service Medal, 1967, of the commissioned corps, USPHS; Distinguished Service Medal, 1971, of the commissioned corps, USPHS; and publication of 48 papers on infectious diseases.

Mr. FLOOD. Do you want us to meet some of the people I see with you?

Dr. DAVIS. On my left is Mr. Charles Leasure, Executive Officer of the National Institute of Allergy and Infectious Diseases. On his left is Dr. John Seal, the Scientific Director of the Institute, and Mr. Martin Fuller is next, the Financial Management Officer, and Dr. Alfred Webb is also here in the room.

Mr. FLOOD. All right.

I see you have a prepared statement. How do you wish to handle this?

Dr. DAVIS. I would be glad to read it, Mr. Chairman.

Mr. FLOOD. All right, suppose you do.

OPENING STATEMENT

Dr. DAVIS. Mr. Chairman and members of the committee:

Research efforts are moving on a broad front against infectious, immunologic and allergic diseases and I wish to bring you up to date on several exciting scientific developments. Most of what I have to report has been built on a foundation of painstaking basic research, particularly in the fields of microbiology, immunology, genetics and biochemistry. Results of such research have significance not only for infectious diseases—hepatitis, influenza, meningitis—but also for concerns of other institutes, such as cancer and heart.

HEPATITIS

Last year, I reported that scientists supported by NIAID (1) had "visualized" the virus that causes infectious hepatitis, known as hepatitis A, and (2) had found evidence that the Dane particle was the virus of hepatitis B, sometimes referred to as serum hepatitis.

Mr. FLOOD. For the purpose of the record, since we talked about this last year, would you insert a paragraph or so about the Dane particle you refer to? You don't have to do it right now.

Dr. DAVIS. Yes, we will do that.

[The information follows:]

THE DANE PARTICLE

Techniques have been developed for studying the size, shape, and chemical composition of virus particles. The availability of these techniques has made possible many of the advances in the understanding of hepatitis B virus. Three types of particles associated with hepatitis B have been seen by the electron microscope, concentrated and purified by high speed centrifugation and identified by reaction with specific antibody. These particles are a small sphere, a long tubular structure and a large sphere. The large sphere is called the Dane particle—after its discoverer Dr. Dane of England. It is believed to be the complete virus of hepatitis B. The small spherical and tubular form are apparently viral coat or surface material that is produced in comparatively great amounts by the infected cells of the body. Some of it is assembled in the cell with core antigen to produce the whole Dane particle; but the excess is released free into the blood stream and circulates as the tubes and spheres of surface antigen detectable by the usual serological tests used in screening blood donors.

Dr. DAVIS. Since then, additional evidence has confirmed these two findings, and new techniques have been developed to differentiate between hepatitis A and B. Now, NIAID investigators suggest that there is at least one other hepatitis viral agent that is commonly transmitted by blood transfusions. This suggestion grows out of a study of 22 clinical center patients with post-transfusion hepatitis in whom no laboratory evidence of hepatitis A or B viruses could be found.

Mr. FLOOD. Also Doctor, the distinction between hepatitis A and hepatitis B. Do that for the record.

Dr. DAVIS. Yes, sir.

[The information follows:]

DISTINGUISHING FEATURES BETWEEN HEPATITIS A AND HEPATITIS B

The two infections have nearly the same symptoms; although they are caused by two different viruses. Hepatitis A or infectious hepatitis has a short incubation period—2 to 6 weeks—and the agent appears to be most frequently carried in the feces or stools of infected individuals. In contrast, hepatitis B or serum hepatitis has a long incubation period—6 weeks to 6 months—and is frequently traced to inoculation of blood or blood products from infected persons. There is also evidence that this more serious form of the disease is spread by other means, including the fecal-oral and venereal routes.

Dr. DAVIS. Most recently, Institute scientists have developed a prototype vaccine for the prevention of hepatitis B. It has protected chimpanzees against hepatitis B virus challenge, leading us to believe that we will want to evaluate vaccines of this type in humans at high-risk if extensive animal tests continue to yield unequivocal results. Because of an acute shortage of suitable animal models—chimpanzees for hepatitis B and marmosets, a small South American monkey, for hepatitis A—we are cooperating with the Center for Disease Control and FDA's Bureau of Biologics in establishing breeding colonies for chimpanzees and marmosets in New Mexico and Louisiana.

INFLUENZA AND PNEUMONIA

The institute is supporting work on a variety of experimental influenza vaccines. Within the past year, we established an influenza research center at the Baylor College of Medicine in Texas which will serve as a national focus of research efforts. We hope the data accumulated at Baylor will provide a better understanding of influenza and place us in a better position to combat epidemics of the disease, such as the pandemic forecast for the late 1970's. We also expect to receive important data on influenza research from the Soviet Union as a result of last year's agreement by the U.S.-U.S.S.R. Joint Committee for Health Cooperation. Two of our grantees have already scheduled field and laboratory studies on influenza in the Soviet Union this year, and virus strains used by the Russians in their extensive live vaccine programs have been received by our scientists.

Even in nonpandemic years, influenza and pneumonia together rank fourth among diseases causing deaths in the U.S.

Mr. FLOOD. You might at this point describe what is epidemic and what is pandemic. You better tell us what you mean by epidemic and pandemic. What is the difference. There is a distinction between the two.

Dr. DAVIS. Epidemic refers to a high incidence of influenza occurring in a fairly large region such as a continent or one part of the continent. Pandemic refers to a high incidence throughout the world.

In spite of the availability and use of effective antibiotics, the fatality rate of patients hospitalized with pneumococcal pneumonia has remained high and unchanged for the past decade. Experimental pneumococcal pneumonia vaccines, developed by the Institute, are undergoing field trials in North Carolina and California. Results of these trials should be available within the next 2 years. The Institute is also developing a vaccine against atypical, or mycoplasma, pneumonia, which usually affects young adults. Produced by NIAID contractors at Ohio State and Cornell Universities, this mycoplasma vaccine is undergoing large-scale testing at a Marine Corps facility in South Carolina.

MENINGOCOCCAL MENINGITIS

Meningitis strikes fear in a community because it affects children, is highly contagious, and often leads to permanent neurological damage or death. In an effort to blunt the impact of this disease—particularly in the high-risk group of infants 3 months to 2 years of age—the Institute is evaluating a meningitis vaccine developed originally for Army recruits. Encouraged by limited clinical trials in American children, the Institute agreed to conduct a field trial in Finland where the disease has been quite prevalent. Late last year, 100,000 Finnish children received one of two experimental vaccines to prevent meningitis. All vaccinated children will be carefully followed to determine how many in each group develop later infections, especially during the disease's next peak season.

INFANT DIARRHEA

Infant diarrhea, particularly when combined with malnutrition, is a major cause of death in some countries. This childhood disease is being intensively studied by Institute scientists.

Last year, they identified an agent causing infant diarrhea. Since then, they have been working with scientists at the University of Nebraska and have shown a relationship between this agent of infant diarrhea and a virus which causes a severely debilitating, sometimes fatal disease in newborn calves. They have now developed a diagnostic test, using the calf virus as an antigen, to demonstrate evidence of infection with the human agent. The new test will enable laboratories around the world to diagnose cases of the human disease and will facilitate epidemiologic studies of outbreaks of such infections.

The similarity of the two agents—calf and human—may lead to development of a means for protecting infants against the disease. There is already an oral vaccine to protect calves. If the calf virus is found to infect humans without causing illness, it might be possible someday to immunize against the human disease with a calf virus vaccine! As you know, vaccinia, or cowpox, is used to protect humans against smallpox.

ANTIVIRAL SUBSTANCES

In addition to vaccines, the Institute has stepped up its program to develop substances to treat viral diseases. Scientists are studying the effects of larger-than-normal amounts of interferon—a naturally occurring body substance—on viral infections. They are also developing ways to produce interferon outside the body or to increase the body's production without toxic effects. During the past year, an NIAID scientist has developed a new interferon inducer called poly I.poly C with poly-1-lysine. This new compound is resistant to enzymatic breakdown in the blood of animals and has been found effective in protecting monkeys and chimpanzees against several lethal viruses. Eventually, it may be helpful for patients with serious systemic or respiratory viral infections. At present, NIAID and National Cancer Institute scientists are collaborating in a study designed to determine the possible usefulness of this new compound in treating cancer patients.

Preliminary results in a collaborative study suggest that another antiviral substance, Ara-A—adenine arabinoside—is beneficial in patients with herpes zoster if treated early; however, further evaluation of this drug is needed. A third drug, IDU—iododeoxyuridine—was not effective in treating herpes encephalitis.

VENEREAL DISEASE

With the resurgence of venereal disease, the Institute was encouraged by Congress to intensify our efforts in sexually-transmitted disease research. Our level of funding in this area has increased from $128,000 in fiscal year 1971 to a proposed level of approximately $3 million for 1976. During the past year, we have established our first two large, multiproject programs of venereal disease research at the University of Washington and Harvard University School of Public Health. In addition, the Institute supports 40 grantees, 3 contractors and nearly 20 young scientists who are receiving specialized training related to research on sexually-transmitted diseases. Besides syphilis and gonorrhea, this program is concerned with several other venereal infections, including those caused by herpes simplex virus, mycoplasmas, *trichomonas vaginalis*, cytomegalovirus, chlamydia, and certain fungi.

Mr. FLOOD. Because of the wide lack of knowledge of venereal disease, and particularly confined to gonorrhea and syphilis, for the record will you define, translate, I suppose, each one of those terms other than syphilis and gonorrhea which you mentioned?

Dr. DAVIS. We will be glad to do that.

[The information follows:]

VARIOUS VENEREAL DISEASE INFECTIONS

Investigators in the venereal disease field are becoming increasingly aware of the importance of genital infections other than syphilis and gonorrhea. Microorganisms causing these other infections are described below.

The *herpes simplex virus*, after the initial infection, remains "hidden" in the body, until it is periodically reactivated, causing infections of the skin and mucous membranes. The type 1 strain is responsible for fever blisters and cold sores on the face, near the mouth, while type 2 causes infections below the waist, most commonly of the genital organs. Type 2, believed to be sexually transmitted,

causes painful, temporarily disabling symptoms. This virus is also suspected of being associated with human cancer, particularly cancer of the cervix.

Mycoplasmas, the smallest living organisms capable of reproducing themselves without assistance from other forms of life, are now generally believed to be bacteria. One strain causes atypical pneumonia, and two others have been associated with genital infections in both men and women. These latter two strains may also play a role in septic abortion, infertility, and premature births.

Trichomonas vaginalis is a protozoan parasite found in the genitourinary tract. Vaginal lesions and a discharge are common symptoms in American women, while men are frequently asymptomatic. A common genital infection in the United States, trichomoniasis, as the infection is known, is not usually serious but is personally annoying and costly to the Nation in terms of medical expenses and lost productivity.

Cytomegalovirus, when it infects adults, usually causes no symptoms. Rarely mononucleosis or hepatitis may develop. However, when a fetus is infected with cytomegalovirus through its mother, the resulting congenital infection may cause serious damage and even death.

Chlamydia are a group of microorganisms, currently believed to be related to bacteria. In man, chlamydial infections of the genital tract produce such diseases as lymphogranuloma venereum. There is some evidence that some chlaymdial infections of pregnant women may be transmitted to their children and cause serious eye disease. Certain chlamydia are known to cause infections of the eye, such as trachoma, which may lead to blindness.

Some fungi usually reside in the human body without causing disease. One of these, *Candida albicans*, frequently inhabits the female genital tract, but only rarely that of the male. In females, this fungus sometimes causes an infection known as candidiasis or moniliasis. This is characterized by inflammation and a vaginal discharge. Newborn infants sometimes develop an oral *Candida* infection, thrush, after passing through an infected birth canal.

Mr. FLOOD. There is just no knowledge of those at all, very little. I mean the general public.

Dr. DAVIS. That is correct.

One of the stumbling blocks to syphilis research has been the inability of scientists to grow the causative agent, *Treponema pallidum*, outside of man, the only natural host. A rethinking of this problem has been taking place since a University of Massachusetts grantee discovered that *T. pallidum* consumes oxygen. This finding contradicts the prevailing theory that the organism grows in the absence of oxygen and may lead to success in laboratory cultivation of the organism.

One of the problems of gonorrhea treatment has been the increasing resistance of the gonococcus to antibiotics, such as penicillin. A grantee from the University of North Carolina has now established, for the first time, the basic genetic events involved in the gradual development of resistance to antibiotics. He showed that penicillin resistance is due to the additive effects of mutations of three genes. His findings could be important in designing new drugs.

Another approach to the general problem of resistance to antimicrobial agents is Institute-supported research on plasmids. These are small, transmissible genetic elements in bacteria and are excellent tools of studying how and why microorganisms become resistant to drugs. This genetic engineering is one method used to study one of the most serious medical problems related to hospital-associated infections.

IMMUNOLOGY RESEARCH

Immunology is concerned with the body's protective mechanisms and how they work under normal and abnormal conditions. I believe the NIAID, through congressional support of research and research

training programs, has played a significant role through the years in developing this fundamental science of medicine whose application to disease problems of this and other Institutes expands year by year.

For more than 10 years, NIAID has been at the forefront of transplantation immunology—the scientific matching of donors and recipients for organ transplantation. Standard procedures and materials for tissue matching, developed by NIAID contractors and grantees, and results of work by NIAID-supported scientists on the rejection phenomenon, have helped make organ transplant surgery the treatment of choice for end-stage kidney disease. In 1974, more than 3,500 Americans received kidney transplants—a form of therapy far more cost-effective than hemodialysis.

Also of concern to immunologists are an estimated 35 million Americans who have one or more significant allergies. Since 1971, the Institute has been developing a network of Asthma and Allergic Disease Centers to hasten the translation of knowledge from the laboratory to clinical practice. We now have 17 centers in 13 States. Research interests at these centers include asthma, hay fever, insect allergy, immunodermatology, and hypersensitivity lung disease.

Mr. Flood. What is hay fever?

Dr. Davis. Hay fever is a reaction of the tissues of the nose and eyes to pollens which circulate about in the summertime when plants are pollinating. Actually it doesn't come from hay primarily. It comes from many other plants instead. It is a very old name.

One study, at the NIH Clinical Center, has been concerned with the allergic reaction to cold temperatures. In addition to causing hives, allergy to cold temperatures can also lead to a precipitous drop in blood pressure, fainting, severe shock, and sometimes death. Our scientist has shown that cold urticaria—as it is called—results from the release of histamine from body tissues as they begin to warm up after a cold stimulus. Some experts believe that some unexplained drownings may actually represent cases of allergy where the cold water caused the swimmers to faint, and then drown!

Investigators at our center in Louisiana have developed an experimental animal model for studying hypersensitivity lung disease—an immunologic condition which develops in workers who are exposed to organic dusts in their occupations, such as farmers feeding silage to cows. Using rabbits, the scientists were able to reproduce the lung damage and certain immune responses of the human disease. Results indicate that the insoluble, particle-like nature of the mold antigen is an important factor leading to the production of this lung disease.

Another allergic occupational disease reported recently by a grantee from Oregon is "meat wrappers' asthma". The grantee found two causes of this condition: (1) fumes released when the price labels were applied with heat to the meat packages and (2) polyvinyl chloride fumes released when the plastic wrapping was cut from the supply roll with the hot wire of a wrapping console.

Mr. Flood. Also for the record—you mentioned earlier the allergy reaction to cold temperatures—would you indicate the degrees? What do you mean by cold temperatures that will produce the most probable allergy, at about what degree, and then below that, and so on.

Dr. Davis. Yes, we will do that.

[The information follows:]

COLD URTICARIA

There is no simple answer to this question since many factors are involved in the reactions of cold urticaria patients. The amount and rate of change in temperature, rather than a specific temperature, are most important. This change can take place on any body surface—the outer layer of skin or the surface of the mucous membranes lining, for example, the mouth and throat.

Although the stimulus for the reaction is the drop in temperature, the inflammation, swelling, and hives seem to develop as the body warms up. This rise in body temperature may result from removal of the cold stimulus and through the production of body energy in response to activity.

Cold urticaria reactions usually develop in cold climates, in the winter, after immersion in cold water, after ingesting cold foods or drinks, or after contact with cold objects. The antihistamine, cyproheptadine, is particularly useful in preventing these attacks.

Dr. DAVIS. A grantee from one of our centers in Colorado recently reported that children receiving steroid drugs for intractable asthma appear to run a greater risk of developing cataracts than previously believed. Perhaps a recently reported type of poorly absorbed, inhaled steroid might be a treatment of choice in the future.

Gentlemen, I retire from the Commissioned Corps of the Public Health Service on August 1 after 36 years at NIH. I have been in my present capacity since 1964, and would like to take this opportunity to express to you my warm appreciation for the courtesy and understanding with which you have received my statements. I have always felt great assurance of your support for the goals of our research programs and your personal interest in developing new knowledge that will lead to improved health.

Sometimes all of us are impatient with the progress of medical knowledge, but I am convinced that the surest way to develop it is an unremitting search for the underlying cause and mechanisms of disease in a climate of free-ranging inquiry by men and women of imagination, resourcefulness and perception.

I consider myself privileged to have had a scientific career in an organization that has epitomized these elements under wise leadership and with understanding congressional support.

In conclusion, Mr. Chairman, the budget request for the NIAID for 1976 is $108,711,000. I shall be pleased to try to answer any questions and supply additional information desired for the record.

I have three special reports here which are prepared. One is on clinical immnology, which we mentioned. One is on acute respiratory disease and a third one is on venereal dieases which may have been included in the record from the Center for Disease Control.

Mr. FLOOD. Doctor, I can say this, and I am sure I undoubtedly speak for the committee, that you are a classic example of the imagination, and resourcefulness, and perception which you indicate, which we find all through the Institutes and especially the many times you

appeared before us and testified on these very difficult and extremely interesting presentations that you have made.

I don't like to see you go, but not only do I congratulate you on the many years of service you have given to the country, but I congratulate the country in being so very fortunate as to have you. It works both ways.

Dr. DAVIS. Thank you very much for those kind words.

1976 BUDGET REQUEST

Mr. FLOOD. Doctor, we will give you the same opportunity we give everybody else, all the chiefs who have been here from the other Institutes who have testified before you. Tell us what the impact will be on your research programs now if we approve this budget. By that I mean there is a reduction here of $10,658,000. So what?

Dr. DAVIS. This will have a very serious effect on the research programs. It will make it very difficult to initiate any new ventures at all. We will be severely strained to keep the ongoing programs at a productive and effective level.

Mr. FLOOD. Do you have enough money in your budget to fund all of your noncompeting grants?

Dr. DAVIS. Yes, we do, just barely.

Mr. FLOOD. Just barely. How much money are you going to spend in this budget under the new grants?

Dr. DAVIS. Under this budget?

Mr. FLOOD. Yes.

How does that compare with last year?

Dr. DAVIS. Under this budget we have had to do some recalculation since the rejection of the rescission and we estimate that we would have a little over $1 million for new grants compared to something like $22 million in the current year.

Mr. FLOOD. Suppose we restored your budget to the 1975 level. How many new grants would you be able to fund in 1976?

Dr. DAVIS. We have made a calculation. We estimate that we could fund 175 new grants compared with 375 in the fiscal year 1975.

ECONOMIC IMPACT OF INFECTIOUS DISEASES

Mr. FLOOD. Do you have any kind of an estimate at all as to what it costs this country to treat infectious diseases? Don't forget, that includes loss of work. Do you have any estimate at all?

Dr. DAVIS. We have some estimates for individual diseases. For instance, we estimate that pneumonia costs up to $100 million a year to treat in hospitals. We have estimates for work lost from upper respiratory infections, which is something like $4 billion a year. This is indirect costs. I could supply more for the record.

Mr. FLOOD. All right; do that.

Dr. DAVIS. For a few diseases in which they have been calculated.

[The information follows:]

COST OF INFECTIOUS DISEASE IN THE UNITED STATES

An answer to this comprehensive question is difficult to formulate because estimates of cost have been performed for only a limited number of the more

important disease categories and such estimates do not always use the same techniques and assumptions for arriving at cost estimates. Contrary to the popular view, infectious diseases are still a very important cost of health care. Over 21 percent of all visits to practicing physicians for all purposes were for care of infectious diseases. In another study of family practice the two most common conditions for which patients sought care were infectious—upper respiratory infection and laryngitis; while of the 14 most common conditions, seven were infectious.

National health data indicate that influenza and pneumonia account for more days of bed disability than any other medical condition; upper respiratory conditions, which are mostly infectious or allergic, are second; and heart disease is third.

If days lost from work are costed out, national data estimate that in 1972 infective and parasitic diseases cost nearly $636 million and respiratory conditions including influenza and pneumonia cost $4.8 billion. In the epidemics of 1963, 1966 and 1969 influenza alone is conservatively estimated to have cost the United States $1.7 to $3.9 billion per year.

It is not uncommon for a patient admitted to a hospital to develop an infection after his admission. Such hospital associated infections are the cause of much pain, disability, extra medication and days of hospitalization. The cost of postoperative hospital infections in the United States including lost wages has been estimated as high as $9.8 billion annually.

TEST FOR GONORRHEA

Mr. FLOOD. Last year you told us quite a good deal about an exciting research advance concerning a promising blood screening test for gonorrhea.

What is the status of that test? You made quite a big thing about that.

Dr. DAVIS. Actually there have been two new tests developed within the last few years. The test I spoke about last year is known as a radio immune assay test which is a fairly complicated procedure which can be simplified. It has been worked out by a group at the Rockefeller Institute and by one of their associates who is now at the University of Utah.

It has now been confirmed that this test is extremely useful in identifying disease in women and men who have no symptoms, which, of course, has been one of the principal sources of new infections in gonorrhea.

The second test is one which has just recently been developed at the University of Pennsylvania Hospital by Dr. Morton. It is a simpler test known as a hemagglutination test whereby specific antibodies are used. It has not yet been extensively studied.

However, it has a good deal of possibilities. So there is quite a bit of work going on in this.

COORDINATION OF VENEREAL DISEASE EFFORT

Mr. FLOOD. How do you coordinate all of your VD research with the Center for Disease Control? CDC happens to have a pretty sizable VD prevention program.

Dr. DAVIS. Yes. Our efforts are directed toward developing new fundamental information, primarily about the organisms and the reaction of the body rather than practical applications working with the State and local health departments.

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Our grants are awarded to investigators throughout the country and the world for developing new knowledge which then can be turned into techniques and evaluated and applied.

Mr. FLOOD. How do you coordinate with the Center for Disease Control?

Dr. DAVIS. Whenever we have any meetings we always invite several of their staff members. We read their reports. There is good communication between the Chief of our Bacteriology Branch in the extramural program who looks out for the grants in this area and the head of that program down there.

VENEREAL DISEASE RESEARCH CENTERS

Mr. FLOOD. In your opening statement you told us this past year you established two large multiproject programs for venereal disease research. What about these programs?

Dr. DAVIS. These are attempts to utilize the resources of a fairly large center which is already established and already working and to take a rather broad approach rather than just to study an individual research problem.

They have facilities for developing the technology and evaluating it within one coordinated unit. We think that this will help to translate the results of new knowledge more rapidly. One of them is at a school of public health and the other is at the University of Washington in Seattle where they have a very strong and active program which in itself is closely coordinated with the CDC programs and with the State health department programs.

PRIMATE BREEDING

Mr. FLOOD. In your opening statement you said you were supporting breeding colonies for chimpanzees. I thought that was the responsibility of the Division of Research Resources. You aren't involved in breeding monkeys; are you?

Dr. DAVIS. That is their responsibility for management.

Mr. FLOOD. We appropriate the money to the Division of Research Resources for the purpose of promoting the primate centers.

Dr. DAVIS. That is right. This is their responsibility.

Mr. FLOOD. What about you?

Dr. DAVIS. We can accelerate this for purposes of our programs by providing some additional support for that.

Dr. LAMONT-HAVERS. The Division of Research Resources certainly has responsibility for the primate centers. There has, however, in the last few years been a great crisis in this country because of the lack of availability of many types of nonhuman primates. There are a number of organizations involved, not only the Institute of Allergy and Infectious Diseases and the Division of Research Resources within the National Institutes of Health, but also the Center for Disease Control and the FDA. All of these groups are working together to try to establish breeding colonies for some very specific species but this is outside of the primate centers which are for a different purpose.

INFLUENZA RESEARCH

Mr. FLOOD. In the justifications you indicate there pretty strongly that another epidemic or pandemic maybe is going to strike in the late 1970's. Let us now take a look at that calendar. That is not very far away. What are you doing at least to get this Nation ready for this epidemic? How much are you investing in influenza research? What are you doing about that? You have a red flag up. Here it is. What about it?

Dr. DAVIS. We have progressively increased our investments in influenza research over the last several years with just this point in mind.

For instance, our total program in influenza and other respiratory diseases in 1975 is $3,350,000 and we are hoping to be able to invest about $4 million in 1976.

INFLUENZA VACCINES

Mr. FLOOD. What are you doing to get us ready for this epidemic which is around the corner, the flu epidemic?

Dr. DAVIS. We are continuing to search for new and better vaccines. There are inactivated vaccines which are now being perfected which utilize the new knowledge of genetics of the influenza virus and permit us to combine several strains of virus so that we get the benefits of several strains, for instance, a capability to grow rapidly in embryonated eggs for quicker vaccine production.

Mr. FLOOD. How much of this ammunition is going to be ready to fire when needed?

Dr. DAVIS. We think when this epidemic comes as we expect it that we will have a very much improved influenza vaccine.

Mr. FLOOD. Do you have a crystal ball? How do you know there is going to be an epidemic?

Dr. DAVIS. Epidemics of influenza have come regularly since the 12th century when they were first identified and they have come in this century about every 10 years. You will recall the Hong Kong flu of 1968 and before that the Asian flu of 1957. There was a wide epidemic in 1947 which wasn't particularly severe, thank goodness.

Mr. FLOOD. Then all you have to go by is the calendar like everybody else.

Dr. DAVIS. That is correct, except that we do know the influenza virus is a tricky one. It changes. The antigenetic characteristics of it changes on a continual basis and as its antigens change it develops new antigens to which the population is not immune.

Mr. FLOOD. Even in the course of an epidemic?

Dr. DAVIS. They change prior to the epidemic and then, of course, when a new virus appears to which the population is not immune we have an epidemic. It is one of the few viruses that has this characteristic; very interesting.

BONE MARROW TRANSPLANT

Mr. FLOOD. Last year we talked about bone marrow transplant at some length and its implication for leukemia patients, and you told us

about one-third of the people who actually received the bone marrow transplant were still alive.

Have you been able to improve that survival rate for the recipients of these transplants?

Dr. DAVIS. In leukemia the survival rate of bone marrow transplants is lowest of any of the diseases.

Mr. FLOOD. I am talking about the bone transplant now.

Dr. DAVIS. Yes, bone transplant, and the experience I refer to is 194 transplants during 1974.

Mr. FLOOD. You told us about one-third of the people who received the transplants were still alive when you told us last year.

Dr. DAVIS. Yes. I think it is approximately that now. I say the leukemia patient has the worst prognosis, but patients who have aplastic anemia survive over 50 percent of the time.

MENINGITIS VACCINE

Mr. FLOOD. You also mentioned in your opening statement that you were evaluating a meningitis vaccine. When do you expect that drug to be on the market?

Dr. DAVIS. Actually there is a meningitis vaccine which is licensed now for adults and it is used by the military because of their particular problems. This vaccine was sent to Brazil this last year when they had a very extensive epidemic of meningitis.

Mr. FLOOD. What about on the general market?

Dr. DAVIS. We expect this to be licensed for children within a year or two because it is now undergoing several evaluation studies in children. There is a study in Connecticut and there is also a study in California.

Mr. FLOOD. What are the long-term implications of that drug?

Dr. DAVIS. It should reduce to a very minuscule level the incidence of meningitis in children, and, of course, this is where we are so concerned. There are actually three types. One form is meningococcus. There is another form of meningitis in children caused by hemophilus influenzae which is perhaps even more prevalent and vaccines are being developed for that one also.

We are spending a sizable amount of money on both these diseases. This year we estimate that it will come to about $400,000 and we are really very hopeful that this will make a sizable difference in reducing this disease which can be very severe and can produce damage to the central nervous system and particularly to the hearing, causing deafness.

PNEUMONIA VACCINE

Mr. FLOOD. Last year we talked about a pneumonia vaccine. What is the status of that drug?

Dr. DAVIS. That continues to be extremely promising and it is in the final stages of evaluation. The studies are going on in two centers in this country, one in North Carolina and one at the Kaiser Permanente Institution in California where it is being evaluated in an older population. It takes quite a while to get enough cases in a population to be able to evaluate its effectiveness.

We are glad to say that at least two and possibly three pharmaceutical houses, drug houses, have shown an interest in this vaccine and we

anticipate that they will apply for a license when it is finally evaluated because we think that this could be an extremely important preventive of not only death but illness, particularly in people over 50 years of age.

ASTHMA AND ALLERGIC DISEASE CONTROL

Mr. FLOOD. In your allergy and your asthma centers, do you actually treat people at those places, or do you just engage in research?

Dr. DAVIS. No; they have clinical facilities and they do treat patients.

MEDICAL PRACTICES IMPROVED BY RESEARCH

Mr. FLOOD. You have heard me ask the other doctors this question. What are some of the recent accomplishments developed by your Institute, allergy diseases now, that are routinely used by practicing physicians?

Dr. DAVIS. I would like to mention the treatment of two diseases which are extremely unfortunate diseases but not very common. One is called Wegener's granulomatosis, of which there are very few cases but all are fatal. This has been shown to be effectively treated by a drug known as cyclophosphamide. All was done at the clinical center by our staff there. It is a very useful drug.

Mr. FLOOD. What have you done in the last 2 or 3 years in your Institute that is now routinely being used by the practicing physicians this afternoon?

Dr. DAVIS. Another disease which can be treated, is a much more common disease known as hereditary angioneurotic edema and this has been shown to be treated by a specific chemical. I won't go into the reasons why it helps, and this is available now to all the centers and all the physicians who have cases of this particular disease.

One other, which is still under development, and is used by hospital centers where organ transplantation is done is the production of the tissue typing trays. Nearly every organ transplant that is done now in the United States is with the aid of the tissue typing trays for tissue matching of donor and recipient.

I mentioned earlier the radio immune assay test for hepatitis B, screening of blood donors. It is available commercially and it is inexpensive and is now being widely used throughout the country.

FACILITY FOR VACCINE TRIALS

Mr. FLOOD. Take a look at page 297 of your justifications. There you state that you completed a feasibility study on the development of what you call contractor-operated facilities in order to do trials of live influenza vaccines, cholera toxoid, and other similar vaccines.

Is that a gimmick for getting around employment ceilings? What is that?

Dr. DAVIS. Could I ask Dr. Seal——

Mr. FLOOD. Are you trying to outflank us?

Dr. DAVIS. This is part of our intramural program and may I ask Dr. Seal, who is the Scientific Director, to answer that question?

Dr. SEAL. Mr. Flood, one of the first steps in the development of any new vaccine, when you are ready to take it from the laboratory and put

it in humans, is the very carefully controlled and monitored trial in a reasonably small number of human subjects, usually volunteers, and, as you know, most of the work in the past in this line has been done in prisons.

In the last year or so the Institute has developed a new volunteer facility at the University of Maryland.

Mr. FLOOD. What about the phrase "contractor-operated facilities"?

Dr. SEAL. The University of Maryland has developed and runs this facility for the testing of new vaccines. They work with us in a collaborative way using their staff so it has nothing to do with our ceilings. This testing involves things that we cannot do at NIH.

ADVANTAGES OF A TEST FACILITY

Mr. FLOOD. Does your feasibility study show that it is less expensive to go through that route than through the in-house work done at NIH?

Dr. SEAL. I would say it probably is less expensive for several reasons; although we haven't really tried to compare price. They have a volunteer population, a large number of students at the University of Maryland and other colleges in and around Baltimore, people willing to enlist as volunteers. They have all of the hospital facilities and staff available at this facility for care and treatment of any volunteer and so I would say that it is probably less expensive to do at the University of Maryland than it would be at the NIH clinical center.

Mr. FLOOD. We would like to know a little bit more about that. For the record suppose you give us a summary on that, your findings of the feasibility study report concerning that particular project.

Dr. SEAL. Be glad to.

[The information follows:]

FEASIBILITY STUDY

This refers to a new contract with the School of Medicine, University of Maryland, Baltimore. The NIAID needed a collaborating institution in which initial studies with new candidate, live virus vaccines could be performed using volunteers of various ages and sexes. The feasibility question revolved around capabilities to attract suitable male and female volunteers from nearby colleges or other community elements who were willing and able to be segregated in quarantine for 10- to 30-day periods. Studies of this sort were previously done in prisoners through university contracts or at the District of Columbia Lorton Reformatory. The new facility does not substitute for any previous intramural program and it is not feasible to perform these studies at the NIH because of the lack of suitable populations from which volunteers can be recruited and the money required to create facilities.

GORGAS MEMORIAL LABORATORY

Mr. FLOOD. Doctor, will you describe to the committee the kind of research conducted at the Gorgas Memorial Laboratory down in Panama? How much money do you invest in that lab?

Dr. DAVIS. Of course, I should say that the Gorgas Memorial——

Mr. FLOOD. I am not unacquainted with the Panama situation generally. I am just wondering about the Gorgas Lab now.

Dr. DAVIS. It is funded through a contribution from the Fogarty Center. They study two general kinds of diseases. One is the arthrpod-

borne diseases, diseases transmitted by insects, such as yellow fever. They have made some very interesting studies this last year on a little outbreak of yellow fever that occurred in Panama.

Another insect-borne disease would be leishmaniasis, a disease in tropical areas which has rather severe manifestations of the skin and sometimes of the liver. They also have been studying malaria and have done very extensive studies on the treatment of malaria using some of the new drugs that have been developed over the last few years, experimenting in different primate hosts of which they have quite an assortment down there at the Gorgas Laboratory.

They study Chagas' disease which is caused by a trypanosome and is present only in Central and South America.

Dr. SEAL. They have some work in hepatitis and diarrheal diseases.

Dr. DAVIS. Hepatitis and diarrhea.

Mr. FLOOD. Thank you very much.

Mr. FLOOD. Mr. Michel?

RESEARCH IN THE PRIVATE SECTOR

Mr. MICHEL. Are the various allergies and diseases of interest to your Institute the subject of much research in the private sector?

Dr. DAVIS. Yes. Extensive investigation is conducted by pharmaceutical houses on various drugs which have a beneficial effect on the control and treatment of allergic diseases both in this country and in Europe. Pharmaceutical houses also are engaged in perfecting diagnostic tests after the principles have been established by research, usually supported by this Institute. The Institute attempts to maintain close contact with possible new products and occasionally, when appropriate, has included them in evaluation studies.

GEOGRAPHIC MEDICINE BRANCH

Mr. MICHEL. How much money are you currently spending for programs carried out under the Geographic Medicine Branch?

Dr. DAVIS. For fiscal year 1975 we will obligate approximately $7.6 million for programs of the Geographic Medicine Branch.

Mr. MICHEL. Could you expand upon some of the programs funded under this office?

Dr. DAVIS. The International Centers for Medical Research Program is funded through grants to Johns Hopkins University, University of Maryland, Tulane University, and University of California each of which maintains a working relationship with a research institute in a foreign country. There is an exchange of scientists and faculty members and a mutually agreed-upon research plan by the cooperating institutions. This program provides American physicians and scientists with an opportunity to learn about diseases outside the United States and gives them experience in conducting research in foreign situations.

INTERNATIONAL PROGRAMS

Mr. MICHEL. Dr. Davis, I have been particularly interested by the various programs within all of the Institutes in cooperation with other countries. I note in this Institute that you sponsor a United States-

Japan program which focuses on selected diseases of major health importance to Asia. How much is spent for the specific program?

Dr. DAVIS. The United States-Japan cooperative medical science program is now completing 10 years of a research effort which is uncovering new knowledge of diseases of concern to both the United States and Japan such as tuberculosis, leprosy, cholera, certain parasitic diseases and viral diseases. There are frequent research conferences with both Japanese and American scientists participating, held alternately in Japan and the United States and with mutually agreed-upon research objectives. Each country funds research supported by its own scientists. In 1974, approximately $8 million was spent by the three Institutes supporting this program—allergy and infectious diseases, arthritis, and environmental health sciences. We estimate that essentially the same level will be funded in 1975. Each year a report on this program is transmitted to the Congress.

Mr. MICHEL. What direct benefit do we get from focusing on Asian health problems?

Dr. DAVIS. Many of the diseases included in this program with the Japanese scientists are of importance in the United States such as tuberculosis, rabies, malnutrition and, to some extent, leprosy. The knowledge of other diseases is important to Americans working in Asia and to the diagnosis and treatment of patients returning to this country after having lived abroad.

In addition, there is the possibility of outbreaks of diseases such as cholera and dengue which have caused epidemics in the past and might again in the future. Also, tuberculosis for example, still causes 5,000 deaths and 30,000 new cases annually in the United States.

Mr. MICHEL. Do we have any such international programs which focus on United States health problems specifically?

Dr. DAVIS. Yes. Most United States health problems are also health problems in other countries. For example, we are cooperating with an international program now being established with the Soviet Union on influenza which should facilitate communication with scientists in that country.

Mr. MICHEL. In regard to these international programs such as the United States-Japan program, where is the research done? Do we use the facilities out at NIH or do the Japanese and others have similar facilities?

Dr. DAVIS. Almost all the research in these programs is supported by grants to American medical schools and universities and to some extent in NIH laboratories in Bethesda and the Rocky Mountain Laboratory in Montana. Likewise, the Japanese conduct their research in their own universities, medical schools, and institutions and provide full funding for their own investigators.

"AMERICAN" DISEASES

Mr. MICHEL. Do we have any diseases which are more or less "American" diseases and are most prevalent in this country?

Dr. DAVIS. In general infectious disease is no respecter of national boundaries unless there is some peculiarity in the way reservoirs of a disease exist in nature, say among an animal population, or the way in which it is transmitted, say by mosquitoes. I cannot think offhand

of a major disease problem which could be called a disease of the United States. We do have some diseases which still have a significant incidence that seem to be confined to certain geographic regions. Among these would be Colorado tick fever and Rocky Mountain spotted fever carried by ticks and a series of virus diseases, all apparently dependent upon an unusual mosquito, animal host, human host relationship. These virus diseases would include California and St. Louis encephalitis as well as Eastern equine encephalitis.

MAJOR SUBPROGRAMS

Mr. MICHEL. In your justifications, you state that "the more important problem areas amenable to Federal intervention are called subactivities or subprograms" and you say there are eight of these which currently warrant a relatively high degree of intervention. What are these eight?

Dr. DAVIS. The eight subprograms include the four areas of special legislative concern: asthma and allergic disease centers, venereal diseases, hepatitis, influenza and other viral respiratory infections; plus four others which we see as areas of growing importance, antiviral substances, clinical immunology, hospital associated infections, and research and development on specific disease control measures.

Mr. MICHEL. You also state there are five other areas "which seem more wisely encouraged by a lesser degree of intervention." What are these five?

Dr. DAVIS. These five other areas are the special emphasis programs largely supported by grants. They are called: selective immunologic activation, lymphocyte biology, streptococcal diseases and sequelae, mechanisms of resistance to antimicrobial agents, and chronic and degenerative diseases of man.

ORGAN TRANSPLANTS

Mr. MICHEL. We seem to have been fairly successful with kidney transplants and the results are certainly encouraging. What are the other major organs which show the greatest promise for transplants and how is research in this area coming along?

Dr. DAVIS. Transplants of solid organs, other than kidney, have been made. Worldwide, several hundred hearts and livers have been transplanted with 10% to 20% survival rates, less than 40 lung or pancreas transplants have been made with virtually no survivors. Skin is perhaps the most common transplanted material and, while demanding as regards tissue matching, is relatively easy from a surgical and tissue supply point of view. There is a large potential demand for bone marrow transplants. While the surgical technique and the supply problems are relatively simple, clinical management of the transplanted patient is very difficult probably because the tissue matching is much more complicated than for solid organs.

It is encouraging that survival rates appear to show a progressive improvement and that immunologists are learning more and more about the factors that determine histocompatibility and the different tests that estimate the degree of tissue matching.

Mr. MICHEL. Thank you, Doctor.

Mr. FLOOD. Mr. Conte?

EXPLANATION OF CHANGES WITHIN ACTIVITIES

Mr. CONTE. Dr. Davis, your justification is somewhat deceptive, in that you list increases and decreases for the same activity, research grants, for example. Would you explain why you set tables up this way, and provide a table showing the net increase or decrease for each activity?

Dr. DAVIS. The tables in the justification, such as the summary of changes beginning on page 268, are prepared to show that there are increases and decreases in the same activity. In the case of research grants, the increases represent the conversion of new and competing grants to noncompeting status and the request for additional new and competing grants. The decreases represent those grants that are being terminated or converted to competing status. I will be glad to furnish a table showing net changes included in this budget.

[The information follows:]

NET CHANGE BY BUDGET MECHANISM

	1975	1976	Net change
Research grants	$69,133,000	$59,898,000	−$9,235,000
Training programs	8,960,000	7,934,000	−1,026,000
Research and development contracts	12,888,000	11,686,000	−1,202,000
Direct operations	28,388,000	29,193,000	+805,000
Total	119,369,000	108,711,000	−10,658,000

RESEARCH MANPOWER

Mr. CONTE. What are the academic disciplines from which you draw your researchers?

Dr. DAVIS. Our researchers may have training in medicine, veterinary medicine or any one of a number of basic science disciplines including virology, bacteriology, immunology, parasitology, epidemiology, and biochemistry. Many researchers have more than one degree and all have had some training in several disciplines.

Mr. CONTE. What is the manpower situation in these fields?

Dr. DAVIS. Many of the researchers currently supported by this Institute also received their training support from the Institute, but this is not necessarily so. We tend to train in disciplines that have broad application to medical research so that many of our trainees end up doing research more appropriately supported by other Institutes.

Mr. CONTE. How will the elimination of your training grant program affect the supply of well-qualified manpower for the research carried out in your institute?

Dr. DAVIS. Under the provisions of the National Research Act the National Academy of Sciences will be conducting an in-depth study of research manpower supply and utilization and will be making recommendations regarding manpower needs and shortages in various fields. It would seem premature to comment on these subjects until the National Academy of Sciences report is available.

SPECIAL GRANTS VERSUS REGULAR GRANTS

Mr. CONTE. Would you explain what "special program" research grants are and how they differ from your regular research grant awards?

Dr. DAVIS. Special program research grants are relatively large awards made for a comprehensive approach to a particular subject of research need. We have just two types listed in the budget which are international centers for medical research programs and research career programs. The international centers awards are to universities which have arranged for cooperative studies with institutions overseas on special problems of concern to American scientists. The research careers are awards made to individuals of demonstrated ability or promise to permit them to do practically full-time research in a university.

Although listed under regular grants, we also have a series of centers for the study of asthma and other allergic diseases which brings together high competence in laboratory research in immunology and expert clinical investigation in asthma and other allergic diseases. They differ from regular grants as they are more comprehensive in scope, usually funded at a higher level, and provided with special review procedures before final approval by the Advisory Council.

FELLOWSHIPS

Mr. CONTE. Will you be increasing or decreasing the number of fellowships awarded this year, why and what is the average fellowship award?

Dr. DAVIS. We expect to award 33 new fellowships in fiscal year 1976 compared to 162 in 1975, because so much of the planned budget in 1976 will be required to continue those awarded in 1975. The average fellowship awarded in this Institute will be the same as other Institutes, approximately $10,000 to $14,000 a year for postdoctoral training.

RESEARCH AND DEVELOPMENT CONTRACTS

Mr. CONTE. Will you be awarding more or fewer research and development contracts this year than last year?

Dr. DAVIS. We will be awarding approximately the same number of research and development contracts in 1976 as in 1975.

INCREASE FOR RESEARCH MANAGEMENT

Mr. CONTE. I am interested in the fact that although you have projected a $10 million budget decrease, you have an increase for research management and program services. How do you justify management increases while cutting back on research?

Dr. DAVIS. Research management and program services provides for the coordination and administration of our grants and contracts activities, services rendered by the National Institutes of Health, and the support of my immediate staff in the overall administration, coordination and direction of all the Institute's activities.

The majority of the funds are for personnel compensation and support with the largest other item being the Institute's share of the NIH

management fund. The increase is all for mandatory items such as increased costs of pay, centrally furnished services, and service and supply. There is no program increase in this area.

COORDINATION WITH CENTER FOR DISEASE CONTROL

Mr. CONTE. To what extent does the work done in your institute overlap that done at the Center for Disease Control—it seems that you are duplicating efforts, in venereal disease, for example? Would you clarify this situation?

Dr. DAVIS. Actually, the work done in this institute and the Center for Disease Control overlaps only in attempting to achieve the same broad objectives. Our best contribution to problems of infectious diseases, for example venereal disease, is to develop more fundamental information about the organisms causing the disease and the development of immunity as well as new approaches for treatment and prevention. As this new information emerges it is developed and applied through the CDC in the clinics and the public health departments of the States. There is a special report prepared jointly with the CDC on our programs.

Mr. CONTE. Would you list the diseases with which you and the Center for Disease Control are involved, and describe how your efforts are either complementary or duplicative?

Dr. DAVIS. Similarly, we have common interests in other infectious diseases such as: influenza, hepatitis, meningitis, gastrointestinal infections, dengue fever, and other arthropod-borne viral diseases.

In all cases, NIAID scientists endeavor to search for causes and mechanisms of disease. Research grant awards are made for these same purposes. Members of the staff of CDC participate in our research and planning conferences on these diseases. Reports are exchanged and there is continual scientist to scientist informal communication between the two agencies.

GRANTS VERSUS CONTRACTS

Mr. CONTE. What portion of your research is done on a contractual basis, what portion by grant, and how does this compare to last year?

Dr. DAVIS. Eleven percent of our budget will go for contracts, 62 percent for grants. For fiscal year 1975 the figures are 10 and 65 percent respectively.

Mr. CONTE. Do you have enough project officers to adequately administer your research contracts?

Dr. DAVIS. We have enough project officers to adequately monitor our ongoing activities, but our ability to initiate new contracts is severely restricted by limitations on staff.

Mr. CONTE. In your contracted research, how much of that goes to academic researchers and how much to commercial or industrial researchers?

Dr. DAVIS. If we look at the distribution of the 1975 collaborative research funds to the ultimate recipient—that is the laboratory where the research is performed—our best estimate is about 55 percent to academic institutions, 15 percent to commercial or industrial organizations, and 30 percent to contracts with nonprofit organizations such as

research institutes and State laboratories or to agreements with other agencies.

DIAGNOSTIC MEASURES

Mr. CONTE. Would you describe the progress made during the past year in the development of diagnostic measures, pharmacologic agents, and immunotherapy for allergic patients?

Dr. DAVIS. We have prepared a special report on clinical immunology including allergies which I am submitting for the record.

ALLERGIC REACTION-INDUCING CITIES

Mr. CONTE. A recent newspaper article called Washington, D.C., the worst city in the country for allergy sufferers, because of the combination of high automobile density and large areas of pollen-producing greenery. Do you have national rankings of allergic reaction-inducing cities, and could you list the top 20 or so, along with the bottom 20, if your list extends that long?

Dr. DAVIS. There is no national ranking of allergic reaction-inducing cities. The question of where to move to escape the problems of allergy and asthma is frequently asked of our Institute, but there is no clear-cut answer.

Actually, the first question should be whether to move. The extent of relief to be gained by moving depends, to a great degree, on what is causing the allergy. For the person allergic to house dust or a food, for example, avoidance of these substances will not be accomplished by moving. A change of location will be of most benefit to someone allergic to specific pollens or molds.

Complete avoidance of a particularly troublesome pollen or mold involves moving to another location where the offending substance does not grow. This action disrupts family life and, according to some specialists, may provide only temporary relief. These experts believe that a person with a pollen or mold sensitivity may very well become allergic to a different substance in his new location after sufficient exposure.

For this reason, our Institute suggests that the allergy sufferer first consult his family doctor or an allergist. He can make recommendations about avoiding the allergy-causing substances as much as possible, provide medications to relieve the symptoms of an allergy, and determine whether immunotherapy, commonly known as "allergy shots," would be of help. Only if all these measures fail, should moving be considered.

Once the decision to move is made, the allergy sufferer is faced with the problem of determining a new location. Air pollution, while not a cause of allergy, is indeed an irritant to those with respiratory allergies and asthma and should be considered. Although the Environmental Protection Agency does not have cities ranked by their pollution levels, it can provide data on trends in air pollution levels in various areas.

There is no standard good or bad climate for all allergy sufferers, but climate may be a factor, especially for asthmatics. Again the allergist is best qualified to recommend a specific type of climate for an individual. Given this information, the National Climatic Center in Asheville, N.C., can then tell where such a climate is found.

But, a major problem faced is determining where substances to which a person is allergic do not grow. The American Academy of Allergy's Pollen and Mold Committee receives pollen and mold counts from selected members around the country, but techniques vary and the results are not comparable.

Probably the best way to determine if certain plants grow in a particular locale would be to contact the local chamber of commerce, a practicing allergist in the area, or the State department of agriculture.

INFECTIOUS DISEASES AFFECTING TRANSPLANT RECIPIENTS

Mr. CONTE. Following transplantation, it is often necessary to use immunotherapy to prevent tissue rejection. In many cases the patient then succumbs to an infection such as pneumonia. Is anything being done to develop a substitute immunity for the infectious diseases which seem to afflict transplant recipients?

Dr. DAVIS. The clinical management of immunosuppressed organ transplant patients is a difficult problem. We have three programs of research relevant to this problem. First we have a contracts program on the methods of producing and testing a biological product called antilymphocyte globulin or ALS and an evaluation of its usefulness in kidney transplants. This antiserum tends to prevent the rejection of a transplanted organ by inhibiting the action of the body cells which recognize the organ as foreign material and attempt to destroy it. At the same time the antiserum has minimum interference with the remaining immune systems which deal with bacterial and viral invaders. It is not surprising that these two functions are difficult to separate because the differences in mechanism are not completely understood. Much of our general support for immunological research is devoted to furthering this understanding. Second is the contracts program to develop and evaluate a pneumococcal pneumonia vaccine which could be administered before organ transplant and immunosuppressive therapy to give protection. And third, is our general grants program on the problems associated with hospital-acquired infections. This includes research on a variety of diseases particularly apt to affect patients after they have been admitted to a hospital.

COST TO SOCIETY OF INFECTIOUS DISEASES

Mr. CONTE. Dr. Davis, could you tell me what the cost to society is of the diseases under investigation by your institute?

Dr. DAVIS. There are statistics compiled on this subject but I do not have them with me. I have been asked by the chairman to prepare an insert for the record that will include this information. The data will be made available to you.

BEE VENOM RESEARCH

Mr. CONTE. What sort of research on bee venom do you plan to conduct during 1976 and for what purpose?

Dr. DAVIS. Every year several hundred people die or suffer the life threatening reaction of anaphylactic shock following bee or wasp stings. Two grantees have shown that the bee venom is the allergen

causing the reaction and that individuals can be tested for their specific sensitivity. They are endeavoring to produce a material from purified bee venom which can desensitize such allergic individuals in order to prevent anaphylactic reactions. Our special report on clinical immunology discusses this in more detail.

FUNDING OF ALLERGIC AND IMMUNOLOGIC DISEASES

Mr. CONTE. Your justification refers to the funding of a "reasonable level of new and competing awards" in 1976 for Allergic and Immunologic Diseases. What do you consider a "reasonable level?" How does this compare to last year's level? Would you say that last year's level was unreasonable?

Dr. DAVIS. We feel that the amount is "reasonable" in relation to the overall amount available to the Institute and in relation to scientific opportunities. It actually represents a cut of slightly over $6 million for fiscal year 1975 which was funded "reasonably" based on opportunities then in existence.

Mr. CONTE. If Allergic and Immunologic Diseases were funded at the 1975 level, how would you allocate the increase? Would it all go into new grants, or to continuations, or a combination, or what?

Dr. DAVIS. We would allocate this increased funding between new grants and continuations. We have, for example, a number of our asthma and allergic disease centers coming up for competing renewal. Congress has shown particular interest in this program since its inception a few years ago. We believe that the centers have been a particularly valuable way of blending laboratory and clinical research and of speeding up the translation of research findings into medical care and in setting the highest possible standards of care. It seems important to provide the resources to continue this network of centers.

BACTERIA RESEARCH

Mr. CONTE. Dr. Davis, what would you consider to be the "more adaptable and enterprising bacteria" referred to on page 288 of your justification?

Dr. DAVIS. Many bacteria can be induced in the laboratory to change their relative infectivity or resistance to specific antibiotics. The knowledge that this happens and the way in which it happens is a major part of the concern expressed by investigators at the recent conference on biological hazards at Asilomar in California. But an immediate problem is: "Do such changes happen in nature?" and the answer is clearly "Yes." Among the important bacteria showing increased resistance to antibiotics are the gonococcus, the E. coli group which causes many hospital associated infections, staphylococci, tuberculosis bacteria, and the salmonella group organisms which cause diarrheal diseases.

Mr. CONTE. How much effort are you devoting to research on such bacteria?

Dr. DAVIS. We have a program on the mechanisms of resistance to anti-microbial agents and as of March 1975 we had a portfolio of 35 grants for about $1.7 million.

Mr. CONTE. What are the prospects for such research in the coming year?

Dr. DAVIS. This research should pay off in future years. We may not be able to prevent the development of resistance, but we certainly can be on our guard against the indiscriminate or unwise use of antibiotics and knowledge of how the antibiotic affects the bacterial cell will improve the design of antibiotic drugs and their selection for use in a specific clinical situation.

VENEREAL DISEASE

Mr. CONTE. As your justification states, venereal disease was supposed to be under control some 15 years ago. The fact that it is not would seem to indicate that more effort needs to be put into its eradication, yet you are suggesting a $1 million decrease in venereal disease programs. Can you explain this decrease?

Dr. DAVIS. Revised estimates of our budget indicates that we expect to support about the same amount of research on venereal disease in 1976 as we are in 1975 in spite of the overall reduction in the 1976 request.

HEPATITIS

Mr. CONTE. Your justification says that research toward the control and prevention of hepatitis is now feasible. Does this mean that it hasn't been feasible until this time?

Dr. DAVIS. The history of the prevention and control of nearly all infectious diseases emphasizes the point that when the causative organism can be identified, the specific disease accurately diagnosed and distinguished from other clinically confusing diseases, then epidemiological studies on incidence and methods of transmission can be conducted. Such studies delineate the population at risk and often give clues on how to interrupt the disease transmission. Similarly, as knowledge of how immunity is developed, what is the antigenic structure of the organism and how it can be produced in bulk provide the basis for working seriously toward the development of a vaccine.

Mr. CONTE. What have you been doing the past several years?

Dr. DAVIS. During the past few years, and particularly during the past year for hepatitis A, this knowledge has been developing. We have a brief special report on hepatitis which I would like to submit for the record.

FORECAST OF INFLUENZA OUTBREAKS

Mr. CONTE. Dr. Davis, how do you forecast outbreaks of influenza and how do you know that there will be a pandemic in the late 1970's?

Dr. DAVIS. Influenza epidemics have occurred regularly for many hundreds of years. Since 1933 when the virus was identified epidemiologists have been able to chart them very accurately. Widespread epidemics have been occurring about every 10 years; for example; Hong Kong Flu in 1968, Asian in 1957, a relatively mild outbreak in 1947 and one in the middle of the 1930's. This is due to the fact that the virus changes its antigenetic makeup and becomes virulent since the population has no immunity to the newly developed strains. Of course, we can't predict for certain that there will be a pandemic in the late 1970's but if past experience is a guide, then we should be prepared to deal with one at that time with an improved vaccine and possibly with

some specific treatment. It is to these objectives that our research efforts are directed.

ALLERGIC REACTION TO COLD

Mr. CONTE. In your statement, you mentioned a clinical center study of allergic reaction to cold, and suggested that this may be the cause of some drownings. Is this the sort of thing that should be included in red cross lifesaving courses?

Dr. DAVIS. It is possible that some drownings may be due to allergic reaction to cold water in some individuals. Lifesaving and rescue workers should be alerted to this possibility and to appropriate medications.

DISSEMINATION OF RESEARCH FINDINGS

Mr. CONTE. What actions are you taking to disseminate your research findings into the health-care delivery system?

Dr. DAVIS. Our staff is continually reporting results of its research in major publications—such as The Journal of the American Medical Association and The New England Journal of Medicine—read by practicing physicians.

We also supply research information to controlled-circulation news publications—such as Medical World News and Medical Tribune—which are sent to most of the Nation's physicians.

Our scientists in Bethesda and in Hamilton, Mont., receive several hundred telephone and mail requests for consultation each year from physicians on diagnostic, management, or treatment problems. One specialist in fungal diseases received nearly 200 such requests last year.

Another specialist in rickettsial diseases gave advice to more than 100 physicians, epidemiologists, health department officials and scientists in relation to research on ticks and control of Rocky Mountain spotted fever. These requests came from 20 States. A particularly exemplary effort last year was an educational campaign conducted by this scientist in South Carolina aimed at the medical profession and the general public.

Our Laboratory of Clinical Investigation runs a monthly interinstitution infectious diseases rounds, where practicing physicians from the greater Washington area can learn the latest clinical applications related to infectious diseases. This month's session was on the mycobacterium—the organism which is associated with tuberculosis.

Our research physicians also give numerous lectures at medical schools and teaching hospitals across the country. Their audiences are composed of our future doctors, who will be in practice when the fruits of today's research will be ready for clinical application.

Mr. FLOOD. Thank you very much, gentlemen.

Dr. DAVIS. Thank you.

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Justification of the Budget Estimates

Appropriation Estimate

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

For expenses, not otherwise provided for, to carry out title IV, part D and I of the Public Health Service Act with respect to allergy and infectious diseases, [$119,452,000] *$108,711,000.*

For the "National Institute of Allergy and Infectious Diseases" for the period July 1, 1976 through September 30, 1976, $27,104,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation[1/]

	1975 Estimate[2/]	1976 Estimate
Appropriation	$119,452,000	$108,711,000
Comparative transfers to:		
"Office of the Director, NIH" . . (Transfer of Institutional Relations Branch from Division of Research Grants)	-37,000	---
"Research Resources". . . . . (For rhesus monkey supply program)	-46,000	---
Total, obligations	119,369,000	108,711,000

1/ Excludes the following amounts for reimburseable activities carried out by this account: 1975 - $445,000; 1976 - $445,000.

2/ Excludes 1973 restoration in the amount of $47,000.

Summary of Changes

1975 Estimated obligations	$119,369,000
1976 Estimated obligations	108,711,000
Net change	-10,658,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of pay raise.	---	---	---	$+296,000
2. Within grade increases.	---	---	---	+198,000
3. Wage board pay raise.	---	---	---	+80,000
4. Extra day of pay.	---	---	---	+53,000
5. FTS and postage rate increase.	---	---	---	+22,000
6. Increased cost of service and supply.	---	---	---	+130,000
7. Other Central Services - Program Evaluation and General Expense	---	---	---	+150,000
8. Payment to NIH management fund.	---	---	---	+109,000
Subtotal.				+1,038,000
B. Program:				
1. Research grants				
a. Noncompeting continuations regular program	---	42,102,000	---	+10,460,000
b. Competing grants-regular program.	---	22,055,000	---	+12,867,000
c. Special program	---	4,976,000	---	+2,683,000
2. Fellowships				
a. Noncompeting continuations.	---	1,899,000	---	+1,910,000
b. Competing	---	1,910,000		+500,000
3. Research and development contracts				
a. Noncompeting continuations.	---	9,739,000	---	+3,149,000
b. Competing	---	3,149,000	---	+1,947,000
4. Intramural laboratory and clinical research	---	22,441,000	---	+646,000
Subtotal.				+34,162,000
Total, increases.				+35,200,000

Decreases:

A. Built-in:				
1. Annualization of position reduction	---	---	---	-120,000
2. Nonrecurring items	---	---	---	-759,000
Subtotal				-879,000
B. Program:				
1. Research grants				
a. Noncompeting regular research grants completed or converted to competing status	---	42,102,000	---	-9,730,000
b. Competing regular research grants completed or converted to noncompeting status	---	22,055,000	---	-22,055,000
c. Special programs	---	4,976,000	---	-3,460,000
2. Fellowships				
a. Noncompeting fellowships completed or converted to competing status	---	1,899,000	---	-99,000
b. Competing fellowships completed or converted to noncompeting status	---	1,910,000	---	-1,910,000
3. Training grants				
a. Noncompeting training grants completed or converted to competing status	---	---	---	-1,427,000
4. Research and development contracts				
a. Completed contracts	---	9,739,000	---	-3,149,000
b. Competing contracts completed or converted to noncompeting status	---	3,149,000	---	-3,149,000
5. Intramural laboratory and clinical research	476	---	-6	---
Subtotal			-6	-44,979,000
Total, decreases			-6	-45,858,000
Total, net change			-6	-10,658,000

Explanation of Changes

Increases:

A. Built-in:

The increases will provide: 1. $296,000 for annualization of 1975 pay raise costs in 1976; ($230,000 in intramural and clinical research and $66,000 in research management and program services), 2. $198,000 for

within grade pay increases in 1976; ($108,000 in intramural and clinical research and $90,000 in research management and program services), 3. $80,000 for wage board pay increases in 1976; (intramural laboratory and clinical research), 4. $53,000 for one extra day of pay in 1976; ($38,000 in intramural laboratory and clinical research and $15,000 in research management and program services), 5. $22,000 for increases in Federal Telecommunications System (FTS) and postage; (research management and program services), 6. $130,000 for increases in service and supply costs; ($76,000 in intramural laboratory and clinical research and $54,000 in research management and program services), 7. $150,000 for increases in Program Evaluation and DHEW/NIH General Expense; (research management and program services), 8. $109,000 for increased costs of the NIH Management Fund for centrally furnished services ($179,000 in intramural laboratory and clinical research and − $ 70,000 in research management and program services).

B. Program:

1. Research grants
   a. The amount of $10,460,000 in noncompeting research grants represents increased costs of previously awarded grants plus 168 conversions resulting from grants being made in 1975. Of these figures, allergic and immunologic diseases accounts for $4,065,000 and 64 conversions, and infectious diseases accounts for $6,395,000 and 104 conversions.

   b. The amount of $12,867,000 represents the cost of 183 new and competing renewal research grants for 1976. Of these figures, allergic and immunologic diseases accounts for $5,099,000 and 67 awards and infectious diseases accounts for $7,768,000 and 116 awards.

   c. The amount of $2,683,000 in special programs represents the conversion of competing awards being made in 1975 to noncompeting status in 1976. Of this figure, $170,000 is for allergic and immunologic diseases and $2,513,000 is for infectious diseases.

2. Fellowships
   a. The amount of $1,910,000 in noncompeting fellowships represents the conversion of awards for 108 trainees being made in 1975. Of these figures, allergic and immunologic diseases accounts for $730,000 and 36 trainees and infectious diseases accounts for $1,180,000 and 72 trainees.

   b. The amount of $500,000 represents the cost of funding 33 new trainees in 1976. Of these figures, allergic and immunologic diseases accounts for $180,000 and 12 trainees and infectious diseases accounts for $320,000 and 21 trainees.

3. Research and development contracts
   a. The amount of $3,149,000 in noncompeting contracts represents the conversion of 34 awards being made in 1975. Of these figures, allergic and immunologic diseases accounts for $611,000 and 7 awards and infectious diseases accounts for $2,538,000 and 27 awards.

b. The amount of $1,947,000 represents the cost of funding 21 new awards in 1976. Of these figures, allergic and immunologic diseases accounts for $409,000 and 5 awards and infectious diseases accounts for $1,538,000 and 16 awards.

4. Intramural laboratory and clinical research--The amount of $646,000 will provide for accelerated trials of live influenza and mycoplasma vaccines, cholera toxoid, and other similar vaccines.

Decreases:

A. Built-in:
1. The decreases represent: 1. $120,000 for annualization of savings related to the reduction of 6 positions in 1975 ($120,000 and 6 positions in intramural laboratory and clinical research, 2. $759,000 for non-recurring large equipment items and agreements ($595,000 in intramural laboratory and clinical research and $164,000 in research management and program services).

B. Program:
1. Research grants
a. The amount of $9,730,000 represents approximately 180 noncompeting awards that will be completed or converted to competing status. Of these figures, allergic and immunologic diseases accounts for $4,359,000 and 69 awards and infectious diseases accounts for $5,371,000 and 111 awards.

b. The amount of $22,055,000 represents the completion or conversion to noncompeting status of 380 awards. Of these figures, 168 awards for $10,413,000 will be converted as indicated under Program Increases 1.a.

c. The amount of $3,460,000 reflects the completion or conversion to noncompeting status of special program awards. Of these figures, $301,000 are for allergic and immunologic diseases and $3,159,000 are for infectious diseases.

2. Fellowships
a. The amount of $99,000 represents the funding level of approximately 6 trainees that will be completed in 1975. Of these figures, $58,000 and 4 trainees are for allergic and immunologic diseases and $41,000 and 2 trainees are for infectious diseases.

b. The amount of $1,910,000 reflects the completion or conversion to noncompeting status of awards for 95 trainees. Of these figures, $860,000 and 50 trainees are for allergic and immunologic diseases and $1,050,000 and 45 trainees are for infectious diseases.

3. Training grants--The amount of $1,427,000 represents the funding level of awards for 65 trainees that will be completed in 1975. Of these figures, $206,000 and 10 trainees are for allergic and immunologic diseases and $1,221,000 and 55 trainees are for infectious diseases.

4. Research and development contracts

   a. The amount of $3,149,000 reflects approximately 34 contracts that will be completed in 1975. Of these figures, allergic and immunologic diseases accounts for $409,000 and 5 awards and infectious diseases accounts for $2,740,000 and 29 awards.

   b. The amount of $3,149,000 reflects the completion or conversion to noncompeting status of 34 awards. Of these figures, allergic and immunologic diseases accounts for $611,000 and 7 awards and infectious diseases accounts for $2,538,000 and 27 awards.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
284	Allergic and Immunologic Diseases	---	$32,188,000	---	$28,648,000		$-3,540,000
287	Infectious Diseases. . .	---	58,793,000	---	50,870,000		-7,923,000
296	Intramural Laboratory and Clinical Diseases.	476	22,441,000	470	23,083,000	-6	+642,000
298	Research Mgmt. and Program Services . . .	117	5,947,000	117	6,110,000	---	+163,000
Total obligations		593	119,369,000	587	108,711,000	-6	-10,658,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	593	587	-6
Full-time equivalent of all other positions	60	60	---
Average number of all employees	655	647	-8
Personnel compensation:			
Permanent positions	9,624,000	9,906,000	+282,000
Positions other than permanent	348,000	350,000	+2,000
Other personnel compensation	423,000	445,000	+22,000
Subtotal, personnel compensation	10,395,000	10,701,000	+306,000
Personnel benefits	1,821,000	2,028,000	+207,000
Travel and transportation of persons	412,000	392,000	-20,000
Patient travel	(7,000)	(10,000)	(+3,000)
Transportation of things	75,000	60,000	-15,000
Rent, communications and utilities	380,000	400,000	+20,000
Printing and reproduction	150,000	150,000	---
Other services	3,109,000	3,359,000	+250,000
Payment to NIH Mgmt. Fund	8,843,000	8,952,000	+109,000
Project contracts	12,888,000	11,686,000	-1,202,000
Supplies and materials	2,372,000	2,350,000	-22,000
Equipment	830,000	800,000	-30,000
Grants, subsidies, and contributions	78,093,000	67,832,000	-10,261,000
Insurance claims and indemnities	1,000	1,000	---
Total obligations by object	119,369,000	108,711,000	-10,658,000

Significant Items in House and Senate
Appropriations Committee Report

Item	Action taken or to be taken
1975 House Report	
1. The Committee expects a significant increase in level of research on venereal disease in FY 75. (page 34 of the House Report)	1. Two new venereal disease centers became operational in FY 75 joining the one already in existence. In addition, increased training was supported in this area and new contracts on serological testing will be awarded.
1975 Senate Report	
2. The Committee encouraged new research initiatives in the area of hospital-associated infections. (page 54 of the Senate Report)	2. Funding in this area has increased from $856,000 in FY 74 to approximately $1,450,000 in FY 75.
3. The Committee provided for increased emphasis on the development of vaccines against influenza. (page 54 of the Senate Report)	3. Several promising new vaccines are currently being tested with the hope that one will be available prior to the epidemic expected in the late 1970's.
4. The Committee directs that an additional $500,000 of the Congressional increase be used for the Middle America Research Unit at the Gorgas Memorial Laboratory in Panama to permit uninterrupted operation of the unit through July, 1975. (page 54 of the Senate Report)	4. The Middle America Research Unit has been funded at a level that will ensure its continued operation through fiscal year 1975.

Authorizing Legislation

Legislation	1976 Authorization	1976 Appropriation Requested
Public Health Service Act Section 301--Research and Investigation, in general	Indefinite	
Title IV, Pard D--National Institute of Allergy and Infectious Diseases	Indefinite	$100,777,000[2/]
Title IV, Part I--National Research Service Award Act of 1974	[1/]	7,934,000[2/]

1/ Authorization expires June 30, 1975; extension legislation is proposed.

2/ Funding estimate only.

National Institute of Allergy and Infectious Diseases
Comparable

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
1966	71,164,000	71,164,000	73,733,000	74,111,000
1967	81,064,000	84,011,000	86,011,000	86,011,000
1968	89,014,000	89,014,000	92,107,000	88,998,000
1969	93,190,000	89,747,000	93,747,000	91,468,500
1970	96,417,000	96,417,000	98,908,000	97,722,500
1971	94,739,000	96,412,000	96,912,000	96,412,000
1972	94,765,000	101,430,000	107,150,000	103,517,500
1973	95,614,000	107,647,000	129,233,000	107,647,000 1/
1974	98,667,000	112,718,000	113,974,000	111,063,000 2/
1975	110,321,000	105,760,000 3/	121,917,000	119,369,000
1976	108,711,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

National Institute of Allergy and Infectious Diseases
Actual

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
1966	74,987,000	74,987,000	77,987,000	77,987,000
1967	85,702,000	88,670,000	90,670,000	90,670,000
1968	94,422,000	94,422,000	98,922,000	94,422,000
1969	98,562,000	95,119,000	99,119,000	96,840,500
1970	102,389,000	102,389,000	105,000,000	103,694,500
1971	99,219,000	102,249,000	102,749,000	102,368,000
1972	99,342,000	106,662,000	112,979,000	109,117,500
1973	112,649,000	113,414,000	135,000,000	113,414,000[1/]
1974	98,693,000	112,744,000	114,000,000	111,089,000[2/]
1975	110,404,000	105,843,000[3/]	122,000,000	119,452,000
1976	108,711,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

Justification

National Institute of Allergy and Infectious Diseases

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	593	$12,216,000	587	$12,729,000	-6	$+513,000
Other expenses	---	107,153,000	---	95,982,000	---	-11,171,000
Total	593	119,369,000	587	108,711,000	-6	-10,658,000

General Statement

The NIAID conducts and supports broadly based research and research training on the causes, characteristics, prevention, control and treatment of a wide variety of diseases believed to be caused by infectious agents (including bacteria, mycoplasma, fungi, viruses, rickettsia and parasites, such as protozoa, worms and arthropods), or attributable to allergies or to other deficiencies or disorders in the responses of the body's immune mechanisms.

The Institute's entire spectrum of activities is subsumed under four main headings variously called Activities, Programs or Program Budget Activities.

In its attack on infectious and immunologic diseases the Institute strives: 1) to recognize and define a set of the important national public health problems whose solution would probably be helped by increased research effort; 2) to decide upon the nature and extent of federal intervention in the research process judged most likely to expedite the finding of a solution; and 3) in the long term national interest to support a large body of free ranging, problem oriented, investigator-inspired research and the appropriate research training.

The more important problem areas amenable to federal intervention are called Subactivities or Subprograms. Currently, eight of these warrant a relatively high degree of intervention as characterized by including a collaborative, contract financed, institute coordinated component, one or more portfolios of highly relevant grant supported projects under the direct cognizance of institute staff, a structured communications activity for exchange of data, and a formal apparatus for scientific review and evaluation of portions of the program on a programmatic basis. The collaborative contracts component is conducted in partnership with industry, university research centers, other institutes and federal agencies. Currently, there are five other subactivities or subprograms (called Special Emphasis Programs) which seem more wisely encouraged by a lesser degree of intervention. These are characterized by a portfolio of highly relevant, grant supported projects under the direct cognizance of staff, occasional workshops and

provision for review and evaluation against program goals every three or four years plus a portfolio of related investigator-inspired projects under general staff surveillance in order to be aware and responsive to developments of unusual significance to solving the problems of a subactivity area.

DHEW - National Institutes of Health

CROSSWALK - 1975 Column of 1976 President's Budget

INSTITUTE: National Institute of Allergy and Infectious Diseases
(Dollars in thousands)

Program \ Mechanism	Research Grants			Training Programs		Lab & Clin	R & D	Other Direct	
	Regular Programs		Spec						
	Noncompeting	Competing	Other	Fellowships	Training Grants	Research	Contracts	Oper.	Total
1. Allergic & Immunologic Dis . . .	17,265	8,000	1,405	1,481	1,537	---	2,500	---	32,188
2. Infectious Diseases.	24,837	14,055	3,571	2,328	3,614	---	10,388	---	58,793
3. Intramural Lab & Clin Res. . . .	---	---	---	---	---	22,441	---	---	22,441
4. Research Mgmt & Prog Serv. . . .	---	---	---	---	---	---	---	5,947	5,947
Total obligations	42,102	22,055	4,976	3,809	5,151	22,441	12,888	5,947	119,369

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DHEW - National Institutes of Health

CROSSWALK - 1976 Column of 1976 President's Budget

INSTITUTE: National Institute of Allergy and Infectious Diseases
(Dollars in thousands)

Program \ Mechanism	Research Grants			Training Programs		Lab & Clin	R & D	Other Direct	
	Regular Programs		Spec						
	Noncompeting	Competing	Other	Fellowships	Training Grants	Research	Contract	Oper.	Total
1. Allergic & Immunologic Dis. . .	16,971	5,099	1,274	1,473	1,331	---	2,500	---	28,648
2. Infectious Diseases	25,861	7,768	2,925	2,737	2,393	---	9,186	---	50,870
3. Intramural Lab & Clin Res . . .	---	---	---	---	---	23,083	---	---	23,083
4. Research Mgmt & Prog Serv . . .	---	---	---	---	---	---	---	6,110	6,110
Total Obligations.	42,832	12,867	4,199	4,210	3,724	23,083	11,686	6,110	108,711

National Institute of Allergy and Infectious Diseases

Budget Mechanism

	1975*			1976		
	No.	FTE[1/]	Amount	No.	FTE[1/]	Amount
Grants						
Regular						
Noncompeting	740	---	$42,102,000	728	---	$42,832,000
Competing	193	---	12,900,000	98	---	4,702,000
New	187		9,055,000	85	---	8,115,000
Supplemental	(7)	---	100,000	(4)	---	50,000
Subtotal	1,120	---	64,157,000	911	---	55,699,000
Special						
Scientific evaluation			176,000			176,000
International centers for medical res	4	---	2,400,000	4	---	1,799,000
Research career prog	---	95	2,400,000	---	89	2,224,000
Subtotal	4	95	4,976,000	4	89	4,199,000
Total grants	1,124	95	69,133,000	915	89	59,898,000
Fellowships						
Noncompeting	---	56	1,899,000	---	225	3,710,000
New	---	162	1,910,000	---	33	500,000
Subtotal	---	218	3,809,000	---	258	4,210,000
Training Grants-noncompeting	---	365	5,151,000	---	300	3,724,000
Intramural laboratory & clinical research			22,441,000			23,083,000
Research and development contracts			12,888,000			11,686,000
Research management & program services			5,947,000			6,110,000
Total			119,369,000			108,711,000

* Excludes 1973 restoration ($47,000)

1/ Full-time equivalents

Allergic and Immunologic Diseases

Authorizing Legislation: Public Health Service Act, Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$32,188,000		$28,648,000		$-3,540,000
Sub activities:						
Asthma and allergic disease centers		4,751,000		3,875,000		-876,000
Clinical immunology		7,703,000		6,751,000		-952,000
Total		12,454,000		10,626,000		-1,828,000
Budget Mechanism:						
Research grants:						
Regular:						
Noncompeting	255	17,265,000	250	16,971,000	-5	-294,000
Competing	122	8,000,000	67	5,099,000	-55	-2,901,000
Special:						
International centers for medical res	--	---	--	---	--	---
Research career program	50*	1,229,000	46*	1,098,000	-4*	-131,000
Scientific evaluation	--	176,000	--	176,000	--	---
Subtotal		26,670,000		23,344,000		-3,326,000
Fellowships	98*	1,481,000	92*	1,473,000	-6*	-8,000
Training grants	112*	1,537,000	102*	1,331,000	-10*	-206,000
Research and development contracts	27	2,500,000	27	2,500,000	--	---
Total		32,188,000		28,648,000		-3,540,000

* Represents full-time equivalents

Introduction:

The most rapidly developing activity in the Institute's program is research on allergy and immunology. Basic science has developed methods of studying the body's responses to infections, to transplantation of organs, and to a variety of insect, food or plant pollen allergies.

Grant Supported Research:

These investigator inspired efforts utilize the disciplines of immunology genetics, molecular biology, biochemistry and cell biology. They are concerned with both immediate hypersensitivity and the longer range delayed immune responses of the body. The Institute supports 17 Asthma and Allergic Disease Centers (including one intramural) engaged in applying basic research accomplishments, particularly in the field of immunology, as well as in biochemistry, genetics and molecular biology, to the better understanding and treatment of allergic conditions. These Centers have been engaged in developing new and improved diagnostic measures, pharmacologic agents and immunotherapy for the more than 35 million allergic patients in the U.S. whose diseases represent major causes of disability, work loss, and absence from school. Centers and regular research projects in asthma and allergic diseases will receive sustained support for their work to develop the necessary scientific personnel and training experience required to move their technologic expertise toward daily patient care.

Closely related to the Asthma and Allergic Disease Centers Program is that of clinical immunology. Immune responses are involved in infectious disease, leukemia and other malignancies and diseases of connective tissues. Control of immune processes is also basic to a successful organ transplantation program. The Institute is developing coordinated efforts in clinical immunology in a few key grantee institutions so that this scientific discipline can be applied to a broader spectrum of patient problems. The specialty of clinical immunology has significance for some part of nearly all of the disease problems for which the Institute has primary responsibility. Most of the competing funds are programmed for the regular research grant budget and are to be divided between investigator inspired research and studies specifically programmed for research on allergic diseases and clinical immunology. The investigator inspired research is necessary to provide a continuing pool of new information for research and development on diagnosis and immunotherapy of diseases of the immune response including connective tissue disease, infectious diseases, allergic and neoplastic diseases. The support for the allergic disease centers will be maintained at approximately the current level. The funds for the new fellowship program will be allocated principally to the more programmed efforts.

Collaborative Research - Asthma and Allergic Diseases:

As part of the NIAID initiatives on research on allergy, the Collaborative Research (contracts) programs have sponsored the production, testing and distribution of highly purified, well characterized antigens derived from ragweed, rye grass and parasitic roundworms. Thanks to new technology these reagents and others now planned for will permit investigators, many at the Asthma and Allergic Disease Centers, to perform their research with well defined materials heretofore lacking. More accurate diagnostic

methods and possibly improved methods of treatment should ultimately result. In FY 1976 it is planned to produce and test reagents for research on bee venoms.

During the past year the program has completed final stages of production of allergens derived from parasitic roundworms and rye grass. Antigens E, K and RA-3, derived from ragweed pollen, are currently being utilized and proving valuable research reagents. In a cooperative study with the World Health Organization and the International Union of Immunological Societies, a project was initiated to develop a fluorescent-labelled, anti-human globulin standard that will ultimately serve as an international standard.

Collaborative Research - Clinical Immunology:

The overall objective of this contracts program is to develop further and more fully utilize existing techniques and reagents and to devise new approaches for improving the survival of transplanted organs and consequently extending the useful lives of recipients. In FY 1976, the follow-up phase will continue on the 100 transplant patients in an evaluation study of the usefulness of antilymphocyte globulin, an immunosuppressive substance.

A more comprehensive, longer range study to evaluate the effectiveness of tissue matching in determining organ graft survival will continue through FY 1976 and will add several hundred new cases toward the projected goal of 3,000 anticipated in FY 1977. Follow-up studies will carry through FY 1979. Also continuing in FY 1976 will be studies to determine new approaches to regulating the immune mechanisms involved in organ transplant survival and the immunopathology of organ rejection.

During FY 1975, the goal of 100 patients needed in evaluation of antilymphocyte serum has been achieved and approximately 700 patients will have been added to the evaluation of tissue matching and the survival of transplanted kidneys derived principally from unrelated cadaver donors. Utilization of common protocols and standard NIH typing trays by a variety of organ transplantation centers throughout the USA has been a major accomplishment in itself and should provide an answer to the critical question - does good matching enhance the survival of cadaver-derived transplanted kidneys.

During the past year standardized reagents were provided to perform cell typing for approximately 3,600 U.S. and 2,400 foreign kidney transplants.

Overall Activity Data:

This activity on allergic and immunologic diseases includes 317 regular research grants at an average cost of $69,000, 46 research career program personnel, 194 trainees and fellows, and 27 contracts at an average cost of $92,000. Lower priority continuation costs, based on program relevance and degree of scientific merit, will not be funded in 1976. A reasonable level of new and competing awards will be maintained in 1976.

Infectious Diseases

Authorizing Legislation: Public Health Service Act, Title IV, Parts D and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$58,793,000		$50,870,000		$-7,923,000
Subactivities:						
Venereal diseases		4,122,000		3,020,000		-1,102,000
Hepatitis		3,000,000		2,150,000		-850,000
Influenza and other viral respiratory infections		4,310,000		4,485,000		+175,000
Disease control measures research & development		11,110,000		10,730,000		-380,000
Antiviral substances		3,356,000		3,000,000		-356,000
Hospital associated infections		1,700,000		1,760,000		+60,000
Total		27,598,000		25,145,000		-2,453,000
Budget Mechanism:						
Research grants:						
Regular:						
Noncompeting	485	24,837,000	478	25,861,000	-7	+1,024,000
Competing	258	14,055,000	116	7,768,000	-142	-6,287,000
Special:						
International centers for medical research	4	2,400,000	4	1,799,000	--	-601,000
Research career program	45*	1,171,000	43*	1,126,000	-2*	-45,000
Scientific evaluation	--	---	--	---	--	---
Subtotal		42,463,000		36,554,000		-5,909,000
Fellowships	120*	2,328,000	166*	2,737,000	+46*	+409,000
Training grants	253*	3,614,000	198*	2,393,000	-55*	-1,221,000
Research and development contracts	113	10,388,000	100	9,186,000	-13	-1,202,000
Total		58,793,000		50,870,000		-7,923,000

* Represents full-time equivalents

Introduction:

Infections, particularly bacterial and viral infections, are a frequent, and for some agents an increasing, hazard to the very young, the aged, the hospitalized and to those who undergo treatments such as cancer therapy which depress their immune system.

While many infectious diseases, particularly viral diseases, have been controlled by vaccines and many others, particularly bacterial diseases, by the familiar antibiotic therapy, there still exist substantial problems. Virtually no effective antiviral therapy is yet available for general use and the more adaptable and enterprising bacteria not only change their relative infectivity through genetic modification but also alter their resistance to antibiotics. The multiplicity of viral diseases is a major contribution to the costs and anguish of ill health. The Institute is concerned with the seemingly mild diseases with their enormous aggregate socioeconomic impact as well as with lethal diseases such as influenza; with the subtle long term role probably played by known and unknown viruses in a series of chronic and degenerative diseases; with the complicated and poorly understood ways in which the body responds to virus infection and generally cures it; with the intricate way in which viruses attack and invade body cells, reproduce and combine viral genetic material with host genetic material to create biological monsters such as cancers.

Parasitic infestations are still common in the U.S. For example, the "worms" in the intestinal tract can cause retarded development and reduced stamina, especially in the young; this is a problem in the lowest socioeconomic segments of our population. Toxoplasma gondii, an organism which infects about one out of seven U.S. citizens, generally with insignificant disease, is apt to cause birth defects in babies born of mothers exposed during pregnancy. Diseases of the traditional tropical variety can be a genuine burden to certain minority populations. These same kind of diseases, particularly malaria and schistosomiasis, continue to be a major health problem in developing countries where the U.S. has important economic and political interest.

Grant Supported Research - Bacterial:

Venereal disease is one of the striking examples of resurgence of a disease thought to have been well under control 15 years ago. Although some of the increase may be related to changes in modern social mores, it also appears that much of the problem relates to the resistance of the causal organisms to antibiotics, the probable emergence of new strains of the gonococcus and the identification of viruses and other classes of infectious microorganisms which can be sexually transmitted. Patient immunity to some types of venereal disease appears to be primarily at the cellular level within the reproductive system. Current research aims include the longer term goal of a better understanding of the body's immune response and the shorter term goal of studying the importance of the various antigens of the gonococcus, especially the pili - minute hairlike appendages - which appear to be potent antigens of possible importance in vaccine development. Further research on the characteristics and adaptive capabilities of the causative organisms will also be essential. During 1976, the venereal disease program will be

continued both in the support of team research through the program project mechanism, and through the training of postdoctoral fellows in the most recent and most promising research methods necessary to control this condition.

The advent of antibiotics has led to an unwarranted sense of security concerning bacterial infections. There are still many problems resulting from resistant organisms and from sequelae of bacterial diseases without effective treatment. Therefore the Institute is greatly concerned with prevention of bacterial disease principally through vaccine development. The diseases under study in this category include meningitis, otitis media, pneumonia due to pneumococci and mycoplasma, cholera, tuberculosis, leprosy and streptococcal infections.

Hospital-associated infections have become a major problem to the health care industry and to the general public, the consumers of health services. The hospital environment is only one facet of this serious problem, but equally important is the patient himself and his altered immune response concomitant with the illness that requires his hospitalization. The Institute's Special Emphasis Program includes research, particularly on the immune response in various illnesses, in poor nutrition, in association with various chemotherapies, and in elderly patients and the very young, as well as epidemiological studies and highly specialized research training. This program will interact with many of the other infectious disease projects supported by the Institute and with the program in clinical immunology.

Viral:

Influenza is a major respiratory disease in terms of morbidity and medical care costs. The influenza virus is readily studied in the laboratory and scientists working on this organism have learned how to manipulate it genetically and to study it in greater depth biochemically in the past year. The current wave of epidemic influenza is associated with a virus that has "drifted" appreciably in antigenic structure from the original Asian strains of 1968 and the vaccine currently recommended and produced commercially has been modified to accommodate for this drift. This drift is in accord with current theories and lends support to the probability that later in the 1970's a new mutant or recombinant will appear and give rise to a serious worldwide epidemic or pandemic. To be ready to deal with this marked change requires vigilance, continuing research and vaccine development.

Identification of the agents for hepatitis A and hepatitis B and the ability to differentiate these organisms have encouraged the Institute to believe that research towards the control and prevention of these diseases is now feasible.

There are currently no broadly effective antiviral substances. However, a few substances effective on selected viruses under special conditions have been identified. These very encouraging results have led to the speculation that many other substances and viruses susceptible to them can be identified. This is prompting the Institute to support both basic research and developmental studies on antiviral substances.

Isolating and defining the role of viruses associated with chronic and degenerative disease is an area in which the Institute continues to apply special emphasis for research support. These diseases require long term investigations.

Clinical virology, which involves the rapid identification of viruses causing illness and the study of their pathogenesis, is becoming increasingly important in the Institute's programs. Clinical virology will be necessary for the appropriate application of antiviral therapy. It already offers opportunity for prescribing correct therapy and the prevention of long hospitalization through accurate viral diagnosis. The Institute sees a need to program new efforts and team research through program projects or center grants during 1976 and a need to increase training efforts in this area.

Parasitic:

The Institute will continue to place special emphasis on immunity to parasites and on the biological regulation of vectors of disease, with particular concern -- in both areas -- for those diseases which are of major worldwide importance. This emphasis is justified in view of the promise which research offers in helping achieve the goals of developing more effective methods for controlling parasitic diseases which afflict man or are transmitted by vectors, usually mosquitoes, ticks or snails.

Parasitic infections generally stimulate an immune response in the body. The enhancing of this response in order to produce resistance to parasitic infections is an important research opportunity in fighting parasitic diseases today. Study of the immune response may not only lead to the development of new means to treat and prevent these diseases, but will also greatly increase understanding of the pathogenesis of these diseases. This program supports considerable fundamental research and we must invest in a few long term training opportunities in order to realize its full potential.

There has been a worldwide concern about the control of insects and other animal parasites through the use of chemicals. As an alternative to chemical control this program is concerned with the development of biological methods of regulating these vectors which will be both effective and much safer than current methods for their control. Genetic manipulation of various animal species and the judicious use of diseases of these parasites or transmitters of disease are offering opportunities for research and application of these methods.

Collaborative Research - Influenza:

The Institute's Collaborative Influenza program now represents an integrated set of contracts encompassing epidemiology, pathogenesis, prevention, and treatment of influenza. In FY 1976, it is anticipated that considerable information will be generated from the numerous contracts awarded in FY 1974 and FY 1975. Evaluation of various experimental vaccines (attenuated live virus vaccine, subunit vaccine, and inactivated neuraminidase-specific vaccine) for safety, antigenicity and efficacy will continue through FY 1976. Success of these trials is dependent on maintaining the supporting network of selected existing contracts.

There are many factors involved which need to be investigated in order to properly understand and control this disease. Toward this end a single Influenza Study Center was initiated this past year which will investigate all aspects of the disease, including epidemiology, immunology, disease pathogenesis, vaccine evaluations and studies on antiviral substances. This critical mass of expertise in many disciplines means that the interrelations of these factors can be evaluated and hopefully lead to more efficient and rapid control of influenza.

During the past year a candidate attenuated virus vaccine (ts-1-E) appeared to be effective in a small number of adults and children. However, mass vaccination imposes very rigid standards for safety in general (including tolerance to the vaccine and resistance of the vaccine strain to reversion towards the wild type), as well as efficacy in protection. To be certain of safety and efficacy, work is continuing to perfect a vaccine by even more careful selection and testing of the candidate virus strains.

A subunit vaccine, consisting of the surface antigens of the influenza virus, was evaluated in normal adult volunteers. The subunit vaccine was shown to be safe, well tolerated and antigenic in the adult volunteers. Work is underway to further purify the subunit components, with the goal of obtaining an even better tolerated and effective vaccine for use in children.

During FY 1975, approximately 1,000 school children were inoculated with either inactivated monovalent influenza A vaccine, neuraminidase-specific vaccine, or placebo. The vaccines were well tolerated. It will take several years to evaluate the protective effects of these vaccines.

During the past year the preparation of monospecific antisera for the hemagglutinins and neuraminidases of both human and animal influenza viruses continued. These reagents are required for the sophisticated analysis of the antigenic composition of human and animal strains, and of newly appearing antigenically "drifted" strains or hybrids.

Collaborative Research - Hepatitis:

This contract supported program has involved close, active collaboration and cooperation with a number of government agencies (CDC, FDA/BOB, Department of the Army and NIH). Recent developments in hepatitis A research including: 1) confirmation by other investigators of the specific identification of the virus by NIAID intramural personnel, 2) development of an animal model system (marmosets), and 3) demonstration of the feasibility of using serological tests for identifying the virus and for estimating the amount of antibody in blood, provide the tools to speed the epidemiological, laboratory and clinical research preliminary to any hepatitis A vaccine development.

Similarly the demonstration of the usefulness of chimpanzees (born in captivity and free of nearly universal hepatitis B infection found in wild caught animals) as a good model of the disease in man will permit testing prototype hepatitis B vaccines for safety and efficacy.

Chimpanzees and marmosets, or more properly tamarins, are the sole experimental animals useful in testing safety and efficacy of prototype hepatitis vaccines. Additionally, the new reagents for assay and diagnosis are derived from them. Unfortunately, these animals are critically limited in supply and so expensive to raise that the rate of vaccine development work will be severely limited.

Nevertheless a prototype vaccine for hepatitis B may well be ready for cautious testing in man by the end of FY 1976 and it may be possible to start preliminary work on a vaccine for hepatitis A. There will be an intensified effort to complete preparation of large lots of hepatitis B candidate vaccine and to conduct comprehensive safety and efficacy tests on these materials. Special efforts will be made to isolate, propagate and more fully characterize the agent of hepatitis A. Because specific tests, however cumbersome, are now available for diagnosis of hepatitis A and B, a start can be made to explore the nature and dimension of the appreciable amount of hepatitis which is due to other agents (presumably viruses).

During the past year a pilot trial of a prototype hepatitis B vaccine, derived from infectious human serum, was conducted in chimpanzees. Results thus far indicate that the highly purified vaccine is safe and is effective in preventing hepatitis B in vaccinated chimpanzees which were subsequently challenged with virulent virus. The recruitment of subjects is nearly complete for the evaluation of the usefulness of hyperimmune gamma globulin in the prevention of hepatitis B in people recently exposed to infection. The evaluation itself will require at least another year. Results of these studies will be coordinated with those from complementary studies sponsored by NHLI. Reagents for various antigenic components of the hepatitis B virus have been prepared and are being distributed worldwide to hepatitis research workers.

Collaborative Research - Venereal Diseases:

The Institute's Collaborative Research program on venereal disease was initiated in FY 1974 with the award of three contracts aimed at laboratory culture of Treponema pallidum, the causative organism of syphilis. These contracts were continued in FY 1975 and new contracts were initiated to develop a serologic typing system for the bacterium which causes gonorrhea, a disease now rampant in the United States with 900,000 reported cases in 1974. Such a serologic system should be useful in epidemiological surveys and hopefully the knowledge of antigenic structure will give some insight as to why individuals are susceptible to repeated attacks. In FY 1976 the above contracts will be continued and new advances exploited as appropriate for improving the diagnosis and treatment of syphilis and gonorrhea.

Collaborative Research - Antiviral Substances:

Collaborative efforts involving a number of contracts in the antiviral substance program will focus on clinical trials to evaluate exogenous interferon in treating a number of life-threatening viral diseases for which there are currently no vaccines available. Interferon will also be tested in treating viral infections in patients whose immune systems have been depressed e.g. by administration of anti-cancer drugs. The trials on adenine arabinoside (ARA-A) in herpesvirus infections of the eye and brain will continue. There will be a continuing effort to seek out and test, first in animal models, other promising candidate antiviral drugs. Once it is established that these drugs are safe and effective, extensive trials in man will be considered. As needed, an appropriate effort to improve on production methodology will be made.

If interferon does indeed prove to be efficacious in treatment of viral disease, better methodologies for its production are needed to bring the cost of treatment down to a more reasonable level. Contracts have indeed been successful in substantially increasing such yields, but the indications are that even greater success can be achieved by a combination of approaches. The antiviral evaluation portion of the program has identified a new antiviral (disodium phosphonoacetate or PAA) which appears to be highly effective against herpesviruses and clinical studies to evaluate its efficacy were initiated in FY 1975. The program was successful in demonstrating that idoxuridine, which was believed to be effective against herpes encephalitis, is not only ineffective but contraindicated. Preliminary results on studies to test the efficacy of ARA-A and interferon against serious viral infections and the painful disease - shingles - are promising, however, final assessment of the studies is still pending.

Collaborative Research Disease Control - Research and Development:

It is expected that the field trials on vaccines to prevent meningococcal meningitis and pneumococcal pneumonia will be nearing completion in FY 1976, although follow-up studies and evaluation of data will need support during this period of time. It is also expected that trials of a special vaccine against the 8 types of pneumococcus most frequently the cause of otitis media, a major cause of hearing loss in children, may be initiated early in FY 1976 and would continue possibly through FY 1977. Antibody response in children given a vaccine for H. influenzae b,(the second major cause of bacterial meningitis in children) will be followed and efforts will be made to produce a more antigenic vaccine by modifying the purification procedure.

Two antituberculosis vaccines will be evaluated further in a primate model. One, an attenuated living cell vaccine, already shown to give greater protection by aerosol than by the normal route of administration, will be evaluated for its duration of protection. Another, a non-viable cell fraction, which does not induce skin test hypersensitivity (and hence does not interfere with the valuable diagnostic tuberculin skin test), will be evaluated in the primate model depending upon the outcome of the present rodent study. Comparative experiments of the two vaccines in the primate model must be accomplished prior to any field evaluation.

The oral administration of cholera toxoid in dogs has produced protection against cholera diarrhea in this animal model. Plans are underway to develop an oral dosage form of cholera toxoid for trials in humans.

Studies to evaluate sulfone related drugs in treatment of leprosy will continue. Immunologic research will include a preliminary trial of transfer factor as a possible treatment and studies of purified soluble antigens derived from M. leprae with a view to developing a rapid diagnostic test and possibly a vaccine for leprosy. The rabies vaccine program will be modified to emphasize the role of viral subunits (particularly the glycoproteins) in the pathogenesis and immune response to vaccination. Additionally the significance and pathogenesis of the exaggerated disease and early death phenomena in vaccinated and experimentally challenged animals will be explored.

The significant accomplishment for the year was the initiation and completion of administration of vaccine in a field trial of 100,000 Finnish children (3 months - 6 years) to determine the effectiveness of Group A meningococcal vaccine. The request from Finland for support of this activity came during the summer of 1974 and the contract was processed and negotiated within a relatively short period of time so that the requisite immunizations could be completed before peak disease season occured. The use of the vaccine in this epidemic is a fortuitous combination of circumstances that provide a definitive field test of mass immunization with the strong probability of substantial benefit to the recipients.

The program was also successful in completing immunization of approximately 7,500 marine recruits of Parris Island at the beginning of their 8 weeks training period with a chemically inactivated vaccine against mycoplasmal pneumonia that was shown to be highly antigenic (and presumably immunizing) in animals. This study will be completed in FY 1976.

During the past year it was found that volunteers immunized by the intranasal route with a vaccine containing type 12 strep M protein were protected against subsequent challenges with live streptococci. This indicates that this antigen could be incorporated into a polyvalent vaccine containing M protein from other common types as a potential vaccine against streptococcal disease.

During the past year, a molluscan cell line has been established from embryos of Biomphalaria glabrata, the snail vector of Schistosoma mansoni. This material will be widely used in multidisciplinary studies of the intramolluscan stages of the schistosome parasite that causes Schistosomiasis - a tropical disease probably next in importance to malaria. Further refinements of technique were developed in the maintenance of human filariasis in small inexpensive animal models.

Overall Activity Data:

This activity on infectious diseases includes 594 regular research grants at an average cost of $57,000, 4 international centers for medical research, 43 research career program personnel, 364 trainees and fellows, and 100 contracts at an average cost of $92,000. Lower priority continuation costs, based on program relevance and degree of scientific merit, will not be funded in 1976. A reasonable level of new and competing awards will be maintained in 1976.

Intramural Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act, Title IV, Part D

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	476	$9,839,000	470	$10,113,000	-6	$+274,000
Other expenses	---	12,602,000	---	12,970,000	---	+368,000
Total	476	22,441,000	470	23,083,000	-6	+642,000

Introduction:

Laboratory scientists and clinical investigators based at Bethesda, Md., and the Rocky Mountain Laboratory, Hamilton, Montana, conduct a broad program of research aimed at the eventual prevention or cure of infections and diseases due to abnormal immune reactions.

The intramural program constitutes a vital bridge between research carried out in other institutions throughout the world and the applied research and development efforts represented by the Institute's collaborative program. Intramural research provides a Federal research base for such efforts as development of vaccines against virus respiratory diseases, hepatitis, and mycoplasma infections and also for the development of antivirals, research reagents, transfer factor therapy and new methods for the diagnosis and treatment of allergy.

Program:

The Clinical Allergic Diseases Center will be further expanded to enable a broader effort for applications of newer knowledge on immunologic processes and tissue mediators to such problems as asthma, urticaria, angioedema, and drug idiosyncrasies. Limitations on outpatient facilities have been partially circumvented by cooperative arrangements with other metropolitan area institutions. This broadened program will include studies on pollen-induced respiratory allergies and allergic skin diseases.

Basic laboratory and clinical investigations continue in fundamental immune processes and in diseases caused by abnormalities in such processes which underlie diseases such as nephritis, rheumatic fever, and lupus erythematosis. This research is closely related and fundamental to efforts in other Institutes such as cancer immunology.

Twenty-five percent of the professional staff are involved in allergic and immunologic disease research.

Virus diseases constitute the single biggest health problem of the American public when measured in dollar costs and days of disability. Intramural research ranges from fundamental studies on the mechanisms of viral replication (which may detect the vulnerable points for the action of antiviral substances), and mechanisms of viral nucleic acid integration

into host cell chromosomes (which can explain late effects expressed as degenerative diseases because of altered host physiology), to clinical trials of antivirals and new vaccines. Institute scientists have played key roles in the rapidly moving progress in viral hepatitis and in the development of a vaccine against hepatitis B. New viruses causing epidemic acute gastroenteritis (winter vomiting disease) and infantile diarrhea have been identified.

NIAID scientists in conjunction with scientists in other Institutes have isolated new viruses associated with tumors and central nervous system disease in man. They have also made recombinant viruses which are useful in probing the mechanism by which viral nucleic acids integrate into the genetic apparatus of host cells and cause the cell to become malignant or otherwise abnormal.

These new viruses and recombinants have unknown but possibly hazardous disease potentials. To work safely with them and to continue this probing by exploiting the new technics and concepts would require specialized containment facilities. Not to continue and indeed expand this work may seriously delay reaching an understanding of the role of virus infections in human cancer.

Thirty-five percent of the Institute's professional staff are engaged in virus research.

Bacterial and mycotic diseases continue to be important causes of death and disability. Patients who receive immunosuppressive drugs in the course of cancer chemotherapy or organ transplantation develop a whole new milieu in which bacteria thrive - both the usual pathogenic types and those of normally low pathogenicity for the usual hospitalized patient. This is reflected in an increasing frequency of infections caused by gram negative bacteria and fungi. Pneumonia is often the killer in patients whose tumors might be considered under control. NIAID's clinical investigators provide consultation services to other Institutes on these problems and engage in a broad spectrum of research on preventive or curative measures ranging from evaluation of new drugs or other modalities of therapy. Other scientists are involved in the development of a vaccine against streptococci and a non-living tuberculosis vaccine.

Among the parasitic and vector-borne diseases that are still problems in the U.S. are Rocky Mountain spotted fever, Colorado tick fever, and the mosquitovectored viral encephalitides. Toxoplasmosis is a significiant cause of eye disease and neonatal mental retardation. Scientists at the Rocky Mountain Laboratory (RML) and Pacific Research Unit are engaged in research on these problems. There is collaboration between RML scientists and health authorities in southeastern states on the rapid diagnosis of Rocky Mountain spotted fever and investigations of what may be a new rickettsial disease.

Other:

Feasibility studies have been completed on the development of a contractor operated facility which would make possible accelerated trials of live influenza and mycoplasmal vaccines, cholera toxoid, and other similar vaccines. Other program increases together with mandatory increases, including NIH management fund total $642,000 over the 1975 level.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Title IV, Part D

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	117	$2,377,000	117	$2,616,000	---	$+239,000
Other expenses	---	3,570,000	---	3,494,000	---	-76,000
Total	117	5,947,000	117	6,110,000	---	+163,000

Included in this activity are the funds and positions required to provide direction, coordination, evaluation and support to the Institute's grant and contract programs and staff assistance to the Director. Also included are funds for the Institute's proportionate share of centrally furnished services such as grounds maintenance, security, utilities, patient care, computer services and communication.

Members of the Institute's senior scientific staff, in collaboration with non-governmental scientists, will plan and develop programs designed to increase our understanding of the basic causes of disease and translate this knowledge into practical application. Technical personnel in this activity will process over 2000 grant applications and approximately 150 contract requests. Also included are Institute responsibilities for financial management, personnel management, scientific and technical information distribution, and administrative support.

Liaison and coordination with other government agencies and non-governmental research facilities here and abroad will continue, parti ularly in hepatitis, venereal disease and influenza.

New more effective means will be sought to communicate the results of research to the researcher, the practicing physician and the lay public. Support will be provided to the National Advisory Allergy and Infectious Diseases Council as well as for other boards, councils and workshops.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Allergic and Immunologic Diseases (PHS Act, Title IV, Part D and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$32,188,000	Indefinite	---	$28,648,000

Purpose: This program conducts and supports research and research training on a wide variety of diseases attributable to allergies or to other deficiencies or disorders in the responses of the body's complicated immune mechanisms.

Explanation: The program accomplishes its objectives through a carefully considered mix of activities supported by selected research project and center grants, fellowship and training awards, and, where the state of the art permits, Federally initiated subprograms, principally of coordinated contract activities.

Accomplishments in 1975: The 17 Asthma and Allergic Disease Centers have begun to evolve a modus operandi that should enable them to fulfill their expected role of being responsive to the important problems in clinical medicine and improving the standards of health care by applying the latest research developments.

Research support under this activity encompassed 357 research grants at an average cost of $70,000, 210 trainees and fellows, and 27 contracts at an average cost of $92,000.

The series of characterized or purified reagents (allergens and selected antisera) useful in studying immunologic diseases has been expanded.

Two evaluation studies (of the immu-osuppressive preparation - antilymphocyte serum - and of the value of tissue typing in transplant of cadaver kidneys) have been started.

Objectives for FY 1976: The annual workshop of the staff of the Asthma and Allergic Diseases Centers will be continued. Encouragement will be given for the undertaking of collaborative approaches to the solution of significant problems in diagnosis and management of allergic diseases.

The battery of immunologic reagents will be expanded.

The two evaluation studies will continue with the one on antilymphocyte serum expected to draw to a close.

Specialized research training will be provided in allergic diseases.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Infectious Diseases (PHS Act, Title IV, Part D and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$58,793,000	Indefinite	---	$50,870,000

Purpose: This program is intended to permit the conduct and support of research and appropriate research training on the causes, characteristics, prevention, control and treatment of a wide variety of diseases believed to be attributable to infectious agents (including bacteria, mycoplasma, fungi, viruses, rickettsia and aprasites, such as protozoa, worms and arthropods).

Explanation: The program accomplishes its objectives through a carefully considered mix of activities supported by research project and center grants, fellowship and training awards, and, where the state of the art permits, Federally initiated subprograms, principally of coordinated contract activities.

Accomplishments in 1975: Research support under this activity encompassed 643 research grants at an average cost of $60,000, 373 trainees and fellows, and 113 contracts at an average cost of $92,000.

Venereal disease research effort was appreciably increased with enlistment of new and competent investigators. Two research centers which permit the blending of laboratory and clinical research became active, as did a limited program of contract supported research and resource development.

Noteworthy in influenza research was the establishment of a center with the range of expertise necessary to work on many facets of this complicated disease. Studies of viral mutation and virus-cell interaction were initiated which should have important long-range significance for vaccine use - especially live attenuated vaccine.

The identification of hepatitis A virus and the development of specific serologic tests and two animal model systems (albeit very expensive) have established the minimum tools necessary for future logical vaccine development.

A prototype hepatitis B vaccine appeared to be safe and effective in preventing infections in vaccinated chimpanzees subsequently challenged with infective virus.

Antiviral drug research continued its difficult task of understanding how virus penetrates, multiplies, and is released from cells - all in the hope that this process can effectively be interrupted without damage to the host cells. Clinical evaluation of several antivirals - interferon, interferon inducers, Ara-A, and IDU - in selected viral diseases was continued. One combination - IDU for herpes encephalitis - appeared, contrary to previous generally held impressions, to be ineffective.

Definite progress was made in the development and clinical evaluation of vaccines for several diseases - bacterial meningitis (meningococcal and H. influenzae), penumococcal and mycoplasmal penumonia and penumococcal otitis media. Other vaccines appeared promising in animals - tuberculosis and cholera.

Objectives for 1976: Intensive contract sponsored efforts to develop a serological typing system for gonococci will be initiated and research grant effort will probe the intricacies of the body's defense mechanisms to infection.

A variety of experimental influenza vaccines (attentuated live, subunit, and inactivated neuraminidase-specific) will enter evaluations for safety, antigenicity or efficacy.

Hopefully, a prototype hepatitis B vaccine will be ready for cautious testing in man. Researchers, generally, can be expected to exploit the newly developed techniques of visualizing and specifically measuring antibody to hepatitis A virus.

Evaluation trials of mass produced interferon, Ara-A and a new antiviral (PPA) will be conducted by the network of collaborating investigators.

A new vaccine against the 8 types of penumococci most important in childhood middle ear infection will enter evaluation studies.

It is expected that a definitive trial of mycoplasmal penumonia vaccine in young men will be completed.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Intramural Laboratory and Clinical Research (PHS Act, Title IV, Part D)

1975 Estimate		1976	1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
476	$22,441,000	Indefinite	470	$23,083,000

Purpose: This program is intended to permit the support of a cadre of highly qualified scientists working in the area of immunologic and infectious diseases. Such a Federal presence in biomedical research aside from its primary function of performing high quality research serves also: to provide officials an essential source of information on, and evaluation of, current scientific opportunities and developments, which is free of vested interest; to provide a source of information and expertise on specific problems and projects to the collaborative (contracts) and extramural (grants) programs; to provide a direct scientist-to-scientist communication link between the Federal establishment and the biomedical research community at large; and to train physicians and other biomedical researchers for senior roles in government and academic research.

Explanation: This program is conducted in laboratories at Bethesda, Md., the Rocky Mountain Laboratory in Hamilton, Montana, and the Pacific Research Section in Honolulu, Hawaii. Program scientists interact in a consultative, advisory and cooperative fashion with scientists of other institutes and government agencies, as well as with private practitioners, academic researchers and Collaborative Research programs.

Accomplishments in 1975: In allergy and immunology, "transfer factor" is being evaluated in the correction of the deficient cellular immunity which underlies chronic candidiasis. The Allergy Center began clinical research on angioedema, urticaria ("hives") and asthma. Purified isolated antigenic components of BCG cell walls have been prepared and (in collaboration with NCI scientists) used in very promising animal studies of "cure" of tumors by immune mechanism. Pulmonary infections with organisms such as Pseudomonas, a frequent cause of fatal pneumonia in immunologically compromised patients undergoing cancer chemotherapy, are being studied. In virus diseases, there is a major effort on vaccine development against influenza, hepatitis and respiratory syncytial (RS) viruses. New knowledge of viral genetics and mutagens has enabled exploration of live vaccines attenuated by introduced genetic defects. Preliminary human trials with such influenza, mycoplasma and RS virus vaccines have been completed with encouraging results. Collaboration between NIAID, CDC and the FDA's Bureau of Biologics has enabled development of sub-human primate models which in turn has allowed identification of the virus and the protective antigen of hepatitis B. A new technique of immune electron microscopy has permitted the first visualization of the viruses of hepatitis A and of epidemic gastroenteritis. Laboratory tests in primates suggest the probable usefulness of a complicated interferon inducing chemical which seems to be resistant to the destructive action of an enzyme in human sera which rapidly destroyed earlier formulations.

Objectives for 1976: To continue program with increased emphasis on better diagnosis and correction of immune disorders and on virus diseases, including antivirals and vaccines.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Research Management and Program Services (PHS Act, Title IV, Part D)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
117	$5,947,000	Indefinite	117	$6,110,000

Purpose: This program provides for the over-all coordination and administration of the Institute's grants and contracts program, services rendered by the National Institutes of Health, and the support of the Institute's Director and his immediate staff in the overall administration, coordination and direction of all the Institute's activities.

Explanation: The majority of the funds are for personnel compensation with the largest other item being the Institute's share of the management fund. Support is provided through contracts for selected scientific meetings and workshops.

Accomplishments in 1975: The Institute continued to review and modify its Special Emphasis and Dollar Allocation Programs to provide support to selected areas of research. Scientific Memoranda, a fast, informal system of communicating research results, were distributed to workers in the area of hepatitis, venereal disease, allergy, leprosy, transfer factor and interferon.

A Manpower Utilization Survey of the contracts management program was carried out and the results have been used as the basis for position distribution.

Catalogs listing research reference materials available from the Institute have been revised and distributed.

Objectives for 1976: This program will continue to provide direction and support for the extramural programs. A Manpower Survey of the grants program and the Office of the Director will be performed with the objective of assisting the new Director in understanding the current organization and making any changes he may desire. Increases emphasis will be placed on the scientific direction of newly developing programs in venereal diseases and hospital associated infections.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation

	1976 Estimate	Interim Budget Period
Appropriation	$108,711,000	$27,104,000
Total, obligations	108,711,000	27,104,000

Obligations by Activity

	1976 Estimate		Interim Budget Period	
	Pos.	Amount	Pos.	Amount
Allergic and Immunologic Diseases	---	$28,648,000	---	$7,003,000
Infectious Diseases	---	50,870,000	---	12,602,000
Intramural Laboratory and Clinical Research	470	23,083,000	470	5,971,000
Research Management and Program Services	117	6,110,000	117	1,528,000
Total obligations	587	108,711,000	587	27,104,000

Obligations by Object

	1976 Estimate	Interim Budget Period
Total number of permanent positions	587	587
Full-time equivalent of all other positions	60	60
Average number of all employees	644	644
Personnel compensation:		
Permanent positions	9,906,000	2,508,000
Positions other than permanent	350,000	88,000
Other personnel compensation	445,000	111,000
Subtotal, personnel compensation	10,701,000	2,707,000
Personnel benefits	2,028,000	507,000
Travel and transportation of persons	392,000	102,000
Patient travel	(10,000)	(---)
Transportation of things	60,000	15,000
Rent, communications and utilities	400,000	100,000
Printing and reproduction	150,000	38,000
Other services	3,359,000	937,000
Payment to NIH Mgmt Fund	8,952,000	2,238,000
Project contracts	11,686,000	2,500,000
Supplies and materials	2,350,000	655,000
Equipment	800,000	200,000
Grants, subsidies, and contributions	67,832,000	17,105,000
Insurance claims and indemnities	1,000	---
Total obligations by object	108,711,000	27,104,000

Justification

National Institute of Allergy and Infectious Diseases

	1976 Estimate		Interim Budget Period	
	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	587	$12,729,000	587	$3,214,000
Other expenses	---	95,982,000	---	23,890,000
Total	587	108,711,000	587	27,104,000

The estimate for the three-month interim period reflects a continuation of the programs of the National Institute of Allergy and Infectious Diseases consistent with the 1976 Estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the 1976 estimate.

THURSDAY, APRIL 17, 1975.

NATIONAL EYE INSTITUTE

WITNESSES

DR. CARL KUPFER, DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DR. WILLIAM F. RAUB, ASSOCIATE DIRECTOR, NATIONAL EYE INSTITUTE
EDWARD H. McMANUS, EXECUTIVE OFFICER, NATIONAL EYE INSTITUTE
KENNETH O. COOKE, BUDGET OFFICER, NATIONAL EYE INSTITUTE
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET
JULIAN M. MORRIS, SCIENTIFIC REPORTS OFFICER

Mr. FLOOD. Now we will continue with the National Institutes of Health.

We have the National Eye Institute. The presentation will be made by Dr. Carl Kupfer, the Director.

We have your biographical sketch which we will place in the record at this point.

[The biographical sketch follows:]

Name: Carl Kupfer, M.D.
Position: Director, National Eye Institute.
Birthplace and date: New York, N.Y., February 9, 1928.
Education: A.B., Yale University, 1948; M.D., the Johns Hopkins Medical School, 1952.
Experience—present: Director, National Eye Institute, NIH. 1966–70: Professor and chairman in Ophthalmology, University of Washington School of Medicine, 1962–66; Assistant professor in Ophthalmology, Harvard Medical School, 1960–62; Instructor in ophthalmology, Harvard Medical School. 1958–60: Research Fellow in Ophthalmology, Harvard Medical School. 1957–58: Research Fellow in Ophthalmology, Wilmer Eye Institute, the Johns Hopkins Medical School; Laboratory assistant biostatistics, the Johns Hopkins Medical School, 1953–54; Laboratory assistant, biostatistics, the Johns Hopkins Medical School, 1952–53; Internship and assistant residency, Wilmer Eye Institute, the Johns Hopkins Hospital.
Association memberships: American Physiological Society; Association for Research in Vision and Ophthalmology; American Academy of Ophthalmology and Otolaryngology; American Ophthalmological Society.
Publications: Author or coauthor of approximately 50 publications in clinical ophthalmology and the anatomy, physiology, and biochemistry of the visual system.

Mr. FLOOD. Do you have some people with you that you want us to meet?

Dr. KUPFER. Yes; I would like to.

On my immediate left is Mr. McManus, who is the executive officer, and to his left is Dr. Raub, who is the Associate Director for extramural and collaborative programs. He has recently joined the National Eye Institute.

Mr. FLOOD. Fine.

Dr. KUPFER. Behind Mr. McManus is Mr. Morris, and he is in charge of the Scientific Reports Office, and then to his right is Mr. Cooke, the Budget Officer.

Mr. FLOOD. You have a prepared statement I see. How do you want to handle it?

Dr. KUPFER. May I present it to you?

Mr. FLOOD. Suppose you do.

Dr. KUPFER. Thank you.

Mr. Chairman and members of the committee, vision is man's most highly developed sense. The visual system, consisting of the eye and nerve pathways to the brain, provides detailed images which are essential for mobility and fulfillment of basic needs. It is our most important source of information for coping with the intricacies of a modern technological society.

The great toll taken each year in the United States by eye diseases is measured, therefore, not in terms of mortality—few disorders originating in the eye cause death—but rather in degrees of physical limitation and financial burden. Yet, such measures are inadequate, for they cannot convey the hardship of functioning without normal vision in a complex environment. It is perhaps for these reasons that a public opinion poll has shown that Americans fear blindness more than any other physical affliction, with the single exception of cancer. Laboratory and clinical research offer hope of significantly reducing the enormous personal and social costs of eye disorders.

VISION RESEARCH PROGRAM PLANNING

To help the National Eye Institute make the most efficient and effective use of its resources for supporting vision research and research training, during the past year and a half a committee of the National Advisory Council, aided by expert consultants and the Institute staff, systematically analyzed and evaluated the current status of vision research support in the United States. The Council's report of this effort, which will soon be published, is the first comprehensive assessment of major needs and opportunities in vision research, one which is expected to have considerable impact on the future course of the National Eye Institute's support in this field.

In each of the National Eye Institute's five major programs—retinal and choroidal diseases, corneal diseases, cataract, glaucoma, and sensory and motor disorders of vision—areas in which current support is judged to be adequate are reviewed. Those in which needs and opportunities warrant increased support are identified, and areas considered important, but for which current support is either minimal or nonexistent, are highlighted. The report also contains an appraisal of vision research training support and an assessment of its importance to the overall program of research on eye disorders.

In making its recommendations for implementing planning activities, the National Advisory Eye Council deliberately avoided developing a national blueprint for vision research. Instead, the Council's recommendations are based on its affirmation of the research grant as the most appropriate mechanism for the support of vision research

and its recognition of the importance of investigator-initiated studies for developing new knowledge in this field. By identifying important areas in which studies should be increased or initiated—rather than specifying projects to be undertaken—and communicating these to the scientific community, the Council hopes that modest shifts and redirections in the course of research will occur as a result of voluntary response by individual scientists to the report's recommendations. This report will be widely disseminated, and there is expected to be a positive response by the vision research community.

CATARACT

One area discussed in the report in which exciting progress is being made and in which major research needs and opportunities exist is that of cataract. Any condition in which a cloudiness or opacity develops in the normally clear lens of the eye, thereby obstructing vision, is called a cataract. In most cases the cause of cataract cannot be determined, but the most common form of the disease is related to processes associated with aging.

More than 3 million people in the United States have cataract. That this disorder should account for so much visual disability is tragic when one considers that cataract removal is one of the most successful major surgical procedures performed today. Yet, because of psychological, social, and economic factors, cataract remains a leading cause of blindness. Approximately 400,000 cataract extractions, costing an average of $2,500 each, including hospitalization, are performed annually, for an estimated total cost of about $1 billion. Discovering means of preventing cataract, and thus alleviating the disability, financial burden, lost productivity, and human suffering associated with this disorder, is therefore a high priority goal of vision research.

In previous years, I have told the committee of significant progress that has been made in determining the cause of certain types of cataracts related to defects in sugar metabolism, and how drugs are being developed that will either prevent or significantly retard the development of these opacities. I can now report on progress being made toward the elucidation of the cause of senile cataract—by far the most common form of this condition.

It has been observed that in aging animal and human lenses, certain proteins in the central region of the lens begin to clump together. This aggregation of lens proteins scatters light, thereby causing the visual disability associated with cataract. Grantees of the National Eye Institute have made progress in developing a means of quantifying and documenting the optical changes in the lens which occur with aging and cataract formation. As a result, the extent and visual effects of the opacity can now be accurately measured and correlated with possible causative factors. This new research technique is an important breakthrough in the clinical, biochemical, and morphologic study of the lens.

Investigators are also investigating the possibility of breaking up the large lens protein molecules in the test tubes. Once this is accomplished, they plan to apply the same methods to the lenses of living animals. If further research shows that protein aggregation is the

cause of senile cataract, it should be possible to develop means of either preventing or slowing the development of this degenerative process.

RETINAL DEGENERATIVE DISEASES

Degenerative disorders of the retina account for more blindness and uncorrectable visual disability than any other cause. Neither a method of prevention nor means of cure has been developed which will effectively deal with senile macular degeneration, a common cause of impaired central vision among the elderly. The same is true for retinitis pigmentosa, a usually hereditary, progressive loss of peripheral visual function which occurs in children and young adults.

For this reason, a considerable amount of research is aimed at elucidating the underlying causes of these disorders. However, only within the past few years have scientists working in this field directed serious attention to the single cell outer layer of the retina called the pigment epithelium.

As a result of newly developed research techniques, investigators have discovered that the pigment epithelium plays a vital role in the visual process. Efforts are now being made to elucidate the key part played by this single layer of cells both in normal retinal function and the development of certain retinal diseases.

One area of great interest is the functional relationship between the photoreceptor cells in the retina and the pigment epithelium. Recent work by a National Eye Institute grantee has shown that the stalk-like outer segments of the rod cells of the retina project into the pigment epithelium. The tips of these cell projections have a normal tendency to break off and the healthy pigment epithelium absorbs these materials. If this absorption does not occur, segments of the broken tips collect between the neural retina and the pigment epithelium forming debris which possibly leads to retinal degeneration. As a result of such findings, a small but steadily growing number of investigators are now directing their research toward determining exactly how the pigment epithelium acts in maintaining the viability of the retina. This work has been greatly facilitated by the recent development of methods for culturing pigment epithelial tissue. We expect that this new research opportunity will be fully exploited and that studies of the pigment epithelium will result in some of the most important contributions to clinical vision research within the next 5 years.

DIABETIC RETINOPATHY

Diabetic retinopathy is now one of the most common causes of new adult blindness. The national Diabetic Retinopathy Study is a controlled clinical trial sponsored by the National Eye Institute which is designed to determine whether photocoagulation can prevent or retard visual loss in proliferative diabetic retinopathy. The study, involving 16 medical centers across the United States, will involve approximately 1,600 patients. As of today, over 1,500 patients have been treated; and, because patient recruitment for some of the participating centers will continue until June 30, we now expect that the study will not only meet its patient recruitment goal, but actually exceed that requirement.

The Diabetic Retinopathy Study incorporates all of the principles of a well-designed and carefully monitored clinical trial of a treatment procedure. Many safeguards to avoid bias, consideration of all possible factors which may influence the outcome of treatment. In addition to careful statistical monitoring, informed consent and ethical concerns have been important considerations in this major research endeavor.

Another new treatment offers hope to those individuals who have already lost vision due to diabetic retinopathy. Called vitrectomy, this procedure involves surgical removal of vitreous which has become clouded by hemorrhage and abnormal blood vessel proliferation. New instruments for vitrectomy have made this delicate procedure practical for the first time, and very impressive results are being obtained in certain cases. Reports that vitrectomy performed before significant loss of vision has occurred may help prevent additional visual loss have led the National Eye Institute to initiate planning of a clinical trial of this procedure in order that ophthalmologists using vitrectomy can be guided by reliable and scientifically obtained clinical research data.

I would like to take this opportunity, Mr. Chairman, if I may to just elaborate a bit more on this procedure because I think it is a very important contribution and I think we will be hearing more about it.

As you recall, if one looks at a section of the eye, the large space between the lens and the retina is filled with a clear jelly material called the vitreous. Normally the vitreous is perfectly clear, but in diabetes blood vessels grow from the retina into the vitreous and these blood vessels leak.

In this particular sequence of events the leakage of a dye can be seen from the blood vessels. Here are blood vessels growing into the vitreous, the dye is injected into the vein and the dye leaks out into the vitreous.

If blood leaks from these blood vessels into the vitreous the blood causes scar tissue to develop so that in a longstanding diabetic patient who has had changes in his retina the vitreous instead of being clear jelly becomes completely opaque and if we look into such an eye we see the white scar tissue.

The new operation of vitrectomy which is done with a cleverly designed instrument enables the surgeon to enter the vitreous cavity through a small incision. This instrument simultaneously puts a sterile salt solution into the cavity and sucks out the fibrous connective scar tissue so that as one moves around this entire cavity all the opaque scar tissue can be removed.

As a result of such an operation an individual who has scar tissue and may only be able to barely perceive light is converted to an individual who has a clear vitreous. The retina behind the vitreous is still functioning and this individual can be rehabilitated to having enough vision so that he can get about and, in some cases, actually go back to a productive job.

This has already proven itself in well established cases where the vitreous is filled with scar tissue. We now propose to test the possibility that using this operation earlier in the course of a disease will prevent this situation from developing.

USE OF VITRECTOMY

Mr. FLOOD. You say that some ophthalmologists are using vitrectomy. Why wouldn't all of them use it?

Dr. KUPFER. This is an extremely difficult operation from a technical point of view and I think that we will see more and more and more ophthalmologists using it.

In the last 4 years that this procedure has been utilized the number of ophthalmologists using it has gone from 1 to about 50 so I think we are seeing a gradual increase.

Mr. FLOOD. Surely all of them are aware of the possibility.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. If they don't do it themselves, they can refer.

Dr. KUPFER. They can refer the patients, yes, sir. We expect that contracts will be awarded during this fiscal year to the initial participants in this study, and that the actual enrollment of patients will begin before the end of the calendar year.

APPLICATIONS OF RESEARCH FINDINGS

In addition to their primary purpose of gaining definitive data on new treatment procedures, clinical trials serve to focus national attention on these discoveries and to provide clinicians with information which can be useful to them in their practice. Thus, clinical trials serve a communications function and facilitate the application of research results.

The National Eye Institute is also engaged in other activities to serve this purpose. Workshops, seminars, and conferences are sponsored on a regular basis to improve communication among scientists in the vision research field. The involvement of the research community in our recent program planning effort greatly enhanced this activity. Special efforts have also been made to communicate new research developments to clinicians through audiovisual presentations and special articles in scientific journals. In a third area, the Institute has actively sought to inform the general public of progress in vision research both to educate the public and to encourage individuals to seek treatment by qualified practitioners. During the coming year, we plan to intensify this activity.

In conclusion, Mr. Chairman, to carry out the programs I have discussed today as well as others designed to prevent and alleviate blindness and visual disability, the National Eye Institute's budget request for fiscal year 1976 is $39,201,000.

I shall be pleased to answer any questions and supply additional information the committee may desire for the record.

BUDGET PROPOSAL

Mr. FLOOD. Doctor, your proposed budget for 1976 calls for a reduction of $4,839,000. Will you be able to find all of your noncompeting continuation grants with this budget?

Dr. KUPFER. Sir, with the 1976 proposed budget we would fall short by about $6.7 million in funding on noncompeting grants.

Mr. FLOOD. How much money would you need to fund all of these noncompeting grants?

Dr. KUPFER. We would need an additional $6.686 million.

Mr. FLOOD. Suppose we were to approve this budget that you present here. Would you be able to fund any new research grants in 1976?

Dr. KUPFER. Yes, sir.

We would be funding approximately $1,211,000 of new research grants.

Mr. FLOOD. Suppose we were to restore your budget back to the 1975 level. How many research grants then would you be able to fund?

Dr. KUPFER. We would be able to fund approximately $4,649,000, which would be about 90 new research grants as compared to 20 research grants.

Mr. FLOOD. How does that compare with the new awards that you funded in fiscal 1975?

Dr. KUPFER. That would be approximately the same, sir.

Mr. FLOOD. In which of those programs would you invest additional money if the committee appropriated additional funds for 1976?

Dr. KUPFER. Sir, first if we look at the program areas we would restore $1.985 million to the retinal and chloroidal diseases area, of which about $1 million would be for diabetic retinopathy research, especially to proceed with this vitrectomy trial that I just mentioned. Additionally, I would restore $256,000 to cataract, $1,394,000 to the cornea program, $120,000 to glaucoma, and $1,212,000 to the sensory-motor program.

Mr. FLOOD. Do you have any estimates at all of the annual income loss due to blindness, actual blindness?

ECONOMIC COST OF VISUAL DISORDERS

Dr. KUPFER. I think if one looks at blindness and visual disability one would have a figure of approximately $1.5 billion.

Mr. FLOOD. Do you have any estimate—of how much public welfare agencies spend each year on services for the blind?

Dr. KUPFER. Yes, sir, $469 million, of which the Federal Government spends $268 million, State governments $131 million, and private agencies $70 million.

Mr. FLOOD. Do you have any idea off the top of your head, a round figure of some kind? If you can find a way to prevent or cure blindness, you are certainly going to reduce substantial payments in welfare services.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. In addition to improving the quality of life for the people affected.

Dr. KUPFER. Yes, sir.

A round figure for support by public welfare agencies and private agencies for the blind would be about a half billion dollars a year.

Mr. FLOOD. That impresses even us.

Dr. KUPFER. And the loss in income is approximately $1.5 billion a year.

RELATIONSHIP BETWEEN VISION RESEARCH AND LENGTH OF HOSPITALIZATION

Mr. FLOOD. In your justification you state that advances in vision research supported by your Institute may lead to a shortening of hospitalization.

Do you have any estimate on how much this amounts to in dollars in savings on an annual basis?

Dr. KUPFER. We would be able to develop figures for the record, sir, but, as you know, one of the major moves in the treatment of ophthalmological problems has been to develop techniques where these problems can be treated on an outpatient basis rather than hospitalizing the individual, so that I think the direction of your question is appropriate in the sense that large amounts of money can be saved by this move.

Mr. FLOOD. We took that question from your statement. There was a shortening of hospitalization in all of these cases.

Dr. KUPFER. I could give you some examples and then I will provide for the record the amount of money.

Mr. FLOOD. All right.

[The information follows:]

Visual impairments rank 12th as a cause of bed disability, 6th in hospital discharges and 10th in hospital days. This is still a great economic burden on the Nation's health care system, but as mentioned earlier, it is an improvement over the earlier impact caused by these diseases. For example as recently as 1964 the hospitalization recommended for cataract surgery was 8–14 days, whereas now the average patient stay is about 4–7 days for the approximately 400,000 cataract operations performed each year. Thus a conservative estimate is that about 100 to 150 million dollars per year may be saved by these research advances. It is probable that there are similar examples of this type saving in other areas of eye care and the National Eye Institute has recently initiated a project which is directed toward documenting these savings with the best economic and statistical data available.

RETINAL DISEASES

Dr. KUPFER. There are types of retinal detachment now that can be treated by the technique of freezing, cryopexy, and this is done as an outpatient procedure. Ten years ago this was not available.

The treatment of diabetic retinopathy using the laser is an outpatient procedure.

Mr. FLOOD. You mention these to an average person and he thinks immediately of an ophthalmologist's office with great big machines and all kinds of lights and what-not and costing fabulous amounts of money, Rube Goldberg settings of all kinds.

Dr. KUPFER. Right.

GLAUCOMA

Mr. FLOOD. What is the basic cause of glaucoma and what do you estimate are the number of people that are afflicted with it each year?

Dr. KUPFER. In the normal eye fluid is being continually produced in the eye and it is continually draining from the eye, maintaining a normal level of pressure. In glaucoma the production of fluid seems to be normal but the fluid cannot leave the eye and, therefore, the pressure begins to build up.

I would say that in glaucoma there probably are in excess of 3,100 new cases a year of people going blind from glaucoma. Glaucoma affects about 1 percent of all the people over the age of 40, so depending on how good the detection techniques are, several hundred thousand patients are newly detected as having glaucoma each year.

Mr. FLOOD. You remember last year you talked about, and let me quote from your statement:

The develpment of methods to grow diseased tissue which causes obstruction to the fluid outflow from the eye to correct trabecular meshwork in tissue culture is under way.

Are you now able to isolate and grow this diseased tissue for further and more complex study?

Dr. KUPFER. Yes, sir.

Mr. FLOOD. What would this mean in terms of actually finding a cure for glaucoma?

Dr. KUPFER. The tissue that we are now growing in tissue culture is the tissue that seems to change and prevent fluid from crossing from inside the eye to outside the eye.

Now, if we can study this tissue not only for normal eyes but from eyes with glaucoma, and this tissue is obtained when we do a surgical operation on a patient with glaucoma, if we can study this tissue I think we may find out how the tissue prevents the fluid from leaving the eye and if we understand that it is possible then to modify the tissue so it does not block fluid leaving the eye.

Mr. FLOOD. In your testimony last year you indicated, and you are saying now, that early detection and treatment is of the utmost importance in controlling glaucoma.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. On page 158 of your justifications you state in glaucoma—

The loss of vision is almost always gradual and without concomitant pain. The portions of the eye involved with peripheral or side vision are usually affected first * * *.

What types of clinical diagnostic screening techniques do you have now or are you building up or developing to assist in the early detection of this glaucoma, this insidious onset?

Dr. KUPFER. The most sensitive technique for diagnosing this loss of side vision is a technique of having the patient determine whether he can see a small spot of light out of the corner of his eye. This is called perimetry or taking a field test.

Now, the problem with this as a diagnostic procedure is that it does require about 45 minutes of time and a patient who can concentrate during this rather long period. Now, there must be better ways developed if one is going to screen a large number of individuals who are at high risk; therefore, we are also developing techniques to photograph the back of the eye, the optic nerve, which we can see.

Mr. FLOOD. Are you developing anything new which will help in determining this early loss of peripheral vision?

Dr. KUPER. Yes, sir.

We now know that certain changes occur in a person's optic nerve about the same time as there is loss of this side vision. We are now supporting research to find the best way to measure these very subtle changes and in this way if such research is successful we can screen large numbers of people by taking a photograph of the back of the eye and then determine which individuals may have loss of side vision and which do not.

RADIOACTIVE MATERIALS

Mr. FLOOD. We have heard a lot of testimony here in connection with biomedical research utilizing minute amounts of radioactive materials. That is to trace both the normal and abnormal functions of the body.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. Is this method of study being used to further the understanding of this flow of liquid within the eyes?

Dr. KUPFER. Yes, sir.

Mr. FLOOD. If so, could that have a greater impact on understanding the mechanisms responsible for what you call the blockage of draining of this eye fluid?

Dr. KUPFER. Yes, sir.

As a matter of fact, these techniques using radioactive materials are being used looking at the tissue that is removed from the glaucoma patient in this outflow channel.

In addition, these radiocative materials are being used to find out why there are changes in the optic nerve when the pressure in the eye increases. Is it an interference with the metabolism of the optic nerve or is it an interference with the blood supply to the optic nerve?

So we are very heavily involved in this type of research.

MARIJUANA DERIVATIVES IN GLAUCOMA RESEARCH

Mr. FLOOD. On Page 159 of your justifications there is mention of a marijuana derivative which may have a beneficial effect in controlling and reducing pressure on the eye.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. What is the story on that?

Dr. KUPFER. The story is that an observation was made approximately 2 years ago that normal volunteers receiving marijuana for other purposes had a fall in their intraocular pressure and with this observation the research has now been extended to laboratory animals and there has been confirmation that the pressure falls and that the reason the pressure falls is that it becomes easier for fluid to leave the eye.

I think the implications are very important because any time we find a drug which helps fluid to leave the eye we want to know what the mechanism is for this.

Mr. FLOOD. How beneficial?

In other words, is there any feeling this could lead to a cure of glaucoma or is it simply one more method of controlling it?

Dr. KUPFER. I would not look toward the use of derivatives of marihuana as a form of treatment. I would look more to these drugs as helping us find out what causes this blockage in outflow and alleviating it. I think there is that possibility of using it as an investigative drug.

CATARACT

Mr. FLOOD. In your opening statement you say that 400,000 cataract extractions costing an average of $2,500 each, are performed annually.

Is there any way in the world to bring down the cost of that operation?

Dr. KUPFER. Sir, this includes the preoperative visits to the ophthalmologist. It includes the hospitalization and postoperative visits and, of course, the surgical fee.

I think the way to bring down the cost is reduce the number of people developing cataracts. I think the prevention of cataracts would have a significant impact, even if we slow down the development of the cataract by 10 years, in other words, if we could slow this down we would cut almost in half the number of patients requiring cataract surgery.

Mr. FLOOD. In your budget justifications, you state that recent research advances suggest that the Eye Institute is on the threshold of a scientific breakthrough that will allow the cataract to be prevented medically.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. What is involved in that and how far away are you from that breakthrough?

Dr. KUPFER. There are two types of cataracts we are discussing.

The first is the cataract that occurs either in patients with diabetes or in infants with a condition called galactosemia. These are infants who are unable to use the mother's milk or cow's milk and they have a number of resultant problems including cataracts.

It is now possible to prevent these cataracts completely in experimental animals with medical means and I think this is a significant breakthrough, but, of course, this is not the type of cataract that is as common as the cataract that accompanies the aging process.

Now our research activities are directed toward this type of cataract and, although I would not specify that we will have a medical cure for this cataract, I think there is now the possibility of medically slowing down the development of this cataract to such an extent that fewer people will have their vision interfered with by the cataract process.

Whether this is going to come about in 5 or 10 or 15 years, I don't think so, but I think it is now a realistic possibility about which we can talk.

DIABETIC RETINOPATHY

MR. FLOOD. Also, in your opening statement you made reference to a national diabetic retinopathy study. What specifically are you doing under the study? What have you learned to date?

DR. KUPFER. First, the study's purpose is to see whether two forms of treatment with very high levels of light—one of which is the laser beam—are beneficial to patients with diabetic retinopathy. These treatments are being widely used but we have never been able to determine whether they are of significant benefit or not.

Therefore, a very careful study is now being done to answer that question. To date we have just completed the enrollment of patients in this study. They have been treated and so far there does not appear to be any difference between eyes of those patients who receive treatment and those patients who do not receive treatment.

Every patient in the study receives treatment, but only in one eye, so we compare the eye that receives the treatment with the eye that does not, and to date there is no difference.

Mr. Flood. How much of your budget do you use for diabetes research every year?

Dr. Kupfer. I think we are funding $4.5 million supporting diabetic retinopathy research.

Mr. Flood. We often talk about problems when we start out with the Institutes, trying to urge different people, and we finally got an Eye Institute.

Now, are you talking about an institute for the right eye, an institute for the left eye? You haven't gone that far have you?

Dr. Kupfer. I used to be amused by that, but now I think it might be a good idea if we could double our budget at the same time.

VISION AIDS

Mr. Flood. I should never have brought that up.

Last year we talked about mechanical seeing aids.

Do you have anything new to report on that device?

Dr. Kupfer. I think I might make two comments.

First of all, the Optacon, a sensing device fitting on a finger which enables blind people to read ordinary print is now in production and a significant number of blind individuals are using it, so it really has left the research phase and is being utilized by the public.

We are also supporting development of a device for converting an optical image to a series of stimuli on the back. That is just entering the evaluation stage and I think in a year or two we will know whether this is a practical way of enabling a blind individual to observe his environment.

SCIENTIST TO PHYSICIAN COMMUNICATIONS

Mr. Flood. Will you tell the committee how you go about communicating all of this new research, all of these new developments, to the practicing physician?

Dr. Kupfer. Yes, sir.

We do maintain a rather active relationship with the practicing physician, mainly through scientific publications, seminars, and direct contact through patient referrals. We have an exhibit highlighting current research each year at the Academy of Ophthalmology which is attended by 60 or 70 percent of all practicing ophthalmologists. We will be having an exhibit at the American Medical Association in June. We do have a large number of fact sheets about eye conditions including recent research developments and do send these out to the practitioner.

PUBLIC INFORMATION ACTIVITIES

Mr. Flood. In your opening statement also you said that the Institute has actively sought to inform the general public now of progress, what we are talking about, in vision research and to encourage individuals to seek treatment by qualified practitioners.

What do you plan to do with the program in fiscal year 1976?

Dr. KUPFER. We want to continue to reach the public by having more publications concerning conditions such as diabetic retinopthy and cataract and glaucoma. I have taken advantage of any opportunities to grant interviews to the press and to popular magazines. We are being involved more in television interviews. We are working with the National Institutes of Health in making film clips that can be put on television throughout the country and radio spots.

DRUG THERAPY OF CORNEAL INFECTIONS

Mr. FLOOD. On page 155 of your justifications you state:

> Infection of the cornea by herpes simplex virus is one of the most important ocular diseases. An antiviral drug (adenine arabinoside) has been found very effective against this disease when applied topically.

Do you have that drug now on the market? Is it available to the practicing physician?

Dr. KUPFER. No, sir, it is not.

However, the practicing physician knows about this and occasionally we receive a phone call from a physician asking us whether it is available or when it will be obtainable and we provide him with this information.

I might say in the short period that we wrote this narrative there is now another drug which is even superior to the adenine arabinoside and this has just completed tests and may be made available soon to the practitioner.

So this is a very rapidly moving field.

Mr. FLOOD. It certainly is.

Mr. Natcher?

Mr. NATCHER. No questions, Mr. Chairman.

Mr. FLOOD. Mr. Michel.

CATARACT REMOVAL COSTS

Mr. MICHEL. In your statement, you mention a figure of $2,500 as the average cost of cataract removals. What costs are involved here? How many days of hospitalization does this include?

Dr. KUPFER. The $2,500 figure includes pre- and postoperative visits to the ophthalmologist, hospitalization and the doctor's surgical fee. Costs representing an average of 4 to 7 days of hospitalization are included.

VITRECTOMY SURGICAL COSTS

Mr. MICHEL. How does the cost of treatment by surgery compare to treatment of the eye by vitrectomy?

Dr. KUPFER. The immediate cause of blindness from diabetic retinopathy is in most cases a hemorrhage into the vitreous humor which does not clear, or the proliferation of fibrovascular tissue from the retina into the vitreous humor which eventually contracts, pulling on the retina and causing retinal detachment. A new surgical technique called vitrectomy has been devised by NEI grantees to treat these problems. In this operation instruments have been developed for gently removing the opaque vitreous from eyes in which hemorrhages have

failed to clear, or for carefully dissecting away most of the fibrovascular membranes. In many cases so treated, definite improvement in visual function has occurred for a short period as long as 4 years. The technique offers the only hope for some eyes with opaque vitreous and is now usually done in eyes which have had only light perception vision for 1 year or longer. This surgical innovation has not been evaluated or standardized as yet and only several hundred of these operations have been performed. Therefore, it is difficult to estimate a uniform fee that might be charged for this treatment, although experience to date shows that sophisticated instrumentation and a high degree of training will be required for those few skillful ophthalmic surgeons who will be qualified to perform this operation.

EYE EXAMINATIONS

Mr. MICHEL. Since blindness from glaucoma can usually be prevented if detected and treated early enough, how often is it advisable to have a regular eye examination?

Dr. KUPFER. All adults, particularly those over age 30 and those with a family history of glaucoma, should have their eyes examined at least every 2 years, preferably once a year. This examination should include procedures for detecting glaucoma.

Mr. MICHEL. How many other eye diseases could be prevented by discovery through regular eye examinations?

Dr. KUPFER. It is easier to deal with almost any eye problem, the earlier it is diagnosed. Even for those conditions which cannot be treated effectively and which may eventually cause blindness early detection can be beneficial in helping the patient adjust to his or her condition and to begin learning new skills for overcoming the handicap of reduced vision. However, there are conditions, in addition to chronic glaucoma which can actually be prevented from causing serious disability if found early. These include acute or angle closure glaucoma, a predisposition which can be detected through careful examination of the eye. This condition can be corrected surgically, thereby curing this form of glaucoma or preventing if from occurring at all. Also retinal detachment, for which there are frequently both early warning signs to the patient and changes which can be observed by the ophthalmologist when looking into the eye, can be prevented by preventive surgery. Early treatment of diabetic retinopathy by photocoagulation is believed by some physicians to be helpful in preventing visual loss from this condition, although this concept is still being evaluated in the cooperative study which the National Eye Institute is sponsoring. Treatment of corneal and conjunctival infections, ocular tumors, and uveitis, are examples of other common eye problems which usually can be ameliorated, if not cured, by early detection and proper treatment. Early detection for amblyopia is essential since treatment for this condition is only generally effective up until the age of five and a half or six.

Mr. MICHEL. Do you have any statistics on how many people avail themselves of regular eye examinations?

Dr KUPFER. The nation's approximately 8,300 actively practicing ophthalmologists see an average of 102 patients each week, or a total

of 846,600 patients for all ophthalomogists a week. The 18,500 optometrists in active practice each see about 43 patients a week for a total of 795,500 patients per week for all optometrists.

EYE-RELATED PHYSICIANS

Mr. MICHEL. What percentage of the population do you estimate does not have access to eye-related physicians?

Dr. KUPFER. There are approximately 4.4 ophthalmologists and about 9.3 optometrists for every 100,000 Americans. Geographical distribution of these practioners varies considerably, with greater concentration in urban areas, as is the case with most health manpower.

Mr. MICHEL. Could a general practitioner adequately give the tests necessary to detect the major diseases which can be prevented? Are eye tests given as regular parts of a general exam by such a doctor?

Dr. KUPFER. General practitioners and internists frequently include tests of visual acuity and ophthalmoscopic examination of the eyes as part of general physical examinations. Some primary care physicians may also check for glaucoma by measuring intraocular pressure. Such screening is extremely valuable but does not substitute for a thorough periodic checkup by an eye specialist.

PRIVATE VISION-RELATED ORGANIZATIONS

Mr. MICHEL. I have seen some pretty good TV spots sponsored by the Society for the Prevention of Blindness? Do you know what kind of a budget they have?

Dr. KUPFER. The total 1974 budget for the National Society for the Prevention of Blindness was $2,600,000. Of this, approximately $35,000 was spent for public education television spots. This is part of an overall expenditure of $1,383,000 for vision health education, approximately 53 percent of the Society's budget.

Mr. MICHEL. What other private groups are active in this area?

Dr. KUPFER. In addition to the National Society for the Prevention of Blindness, other groups which are active in public information campaigns related to vision and visual disorders include the American Foundation for the Blind, Inc.; Lions International; National Retinitis Pigmentosa Foundation, Inc.; American Optometric Association; American Association of Ophthalmology; Blue Cross and Blue Shield. However, I might mention that the National Society for the Prevention of Blindness is one of the most active organizations in public education activities.

INFORMATIONAL ACTIVITIES

Mr. MICHEL. What kind of an effort are you undertaking toward an information program?

Dr. KUPFER. The National Eye Institute already maintains a small but active consumer education program within the Institute's Office of Scientific Reports. Our activities in this area range from answering numerous public inquiries to preparing and distributing consumer education publications. We also have prepared radio and television announcements over the past few years, encouraging people to visit

their eye doctors or inviting them to write to NEI for more information about eye diseases and vision research. The Institute also works with the central NIH Information Office in dispersing educational material about vision disorders and research for inclusion in newspapers, general magazines, and specialized publications for health professionals. If positions are available, we hope to expand this activity during the coming year.

AGING AND THE VISUAL PROCESS

Mr. MICHEL. Since a number of eye ailments appear to be directly related to aging, what kind of input have you had in developing the programs within the new Institute on Aging?

Dr. KUPFER. Members of the National Eye Institute staff have had several discussions with staff of the Institute on Aging. During these discussions, program projects of the NEI related to aging, such as macular degeneration, diabetic retinopathy, glaucoma, senile cataract, and others were identified. It was determined that these programs were only secondarily related to the aging problem, but were directly related to the vision problem. Therefore, they should continue within the purview of the NEI. However, one of the many features that contributes to the uniqueness of the National Institutes of Health is the frequent interdisciplinary collaboration between the several Institutes. Therefore, the NEI looks forward to a continued and useful relationship with the National Institute on Aging. Moreover, it is our understanding that the NIA will serve as the coordinator for the Federal Government on all aspects of the aging process. This assures future cooperation between the NEI and the NIA.

Mr. MICHEL. Thank you.

Mr. FLOOD. Mr. Conte?

PROGRAM PLANNING ACTIVITIES

Mr. CONTE. Dr. Kupfer, could you summarize the conclusions of the National Advisory Council?

Dr. KUPFER. As the result of a review and evaluation of the National Eye Institute vision research program, the following conclusions were derived: Periodic evaluation of the National Eye Institute research program must be undertaken as a first step in assessing ongoing research activities, identifying research needs and opportunities, and determining appropriate support for the National Eye Institute; research program priorities must be established as a means of identifying research needs, delineating research opportunities, and accelerating scientific advances; the National Eye Institute research program planning information concering the goals and objectives of the Institute should be widely disseminated to the research community; communication among research scientists in related fields of investigation should be enhanced to explore basic aspects of, or clinical research facets of, significant visual system diseases; communication with representatives of the Federal Government, the scientific community and the general public should be enhanced; special types of research grants should be developed to encourage applied and clinical research by the grant mechanism; special types of research training programs should

be initiated to assure the availability of an adequate number of fully trained scientists in all areas of basic and clinical investigation; there should be selective utilization of the research contract to augment and extend the research program of the National Eye Institute; the Institute's intramural research program should be strengthened to address newly emerging areas of research, including areas of investigation that require close coordination with the several categorical NIH Institutes; biometrical and epidemiological information regarding vision disorders and blindness should be assembled; special programs of public information regarding vision disease to create public awareness of vision problems in the United States and subsequently improve the overall level of vision care should be emphasized; demonstration projects related to the prevention, diagnosis, and treatment of visual system disease should be developed to accelerate application of research products to the prevention and alleviation of visual system diseases; and consideration should be given to long-term budget requirements to implement the Council's comprehensive plan for the improvement of vision care, including funding of the 24 priority areas of research set forth in the plan.

ASSISTANCE TO THE BLIND

Mr. CONTE. How much money does the Federal Government spend on assistance to the blind each year?

Dr. KUPFER. According to our latest statistics which were compiled in 1971, the Federal Government spends approximately $268 million on assistance to the blind each year.

GLAUCOMA

Mr. CONTE. Have there been any recent advances in diagnosing glaucoma? What about glaucoma treatment?

Dr. KUPFER. Open- and closed-angle glaucoma can now be rapidly and accurately differentiated by means of gonioscopy, a technique perfected by NIH grantees.

Very early visual changes from glaucoma can now be detected by means of improved techniques, such as perimetry, developed by NIH grantees, for measuring the visual field. However, such techniques are time consuming. Consequently, recent emphasis has been on earlier detection before visual-field loss occurs by direct visualization of the optic nerve. Careful studies of the contour and configuration of the optic nerve may identify high-risk individuals for early treatment.

Other recent findings by NEI-supported scientists indicate that glaucoma patients may have an increased lymph cell sensitivity to steroid drugs. This raises the possibility that glaucoma is more than just an eye disease and may have systemic manifestations.

The prevalence of closed-angle glaucoma, curable if detected early, has been reduced; and treatment of the chronic open-angle type has been changed from primarily surgical to primarily medical through the introduction, by investigators supported by NIH, of systemic carbonic anhydrase inhibitors and topical adrenergic drugs. These drugs have markedly decreased the loss of vision caused by chronic glaucoma and reduced the cost of care.

In an effort to improve the delivery of pressure-lowering drugs to the eyes of glaucoma patients, NEI grantees have successfully demonstrated the use of the Ocusert, a thin plastic wafer impregnated with medication which is inserted under the lower lid. Recently approved by the Food and Drug Administration for general use, the Ocusert offers delivery of medication in a manner which is potentially more comfortable and convenient for the patient and which may be more effective in the treatment of disease.

For those cases of glaucoma which are poorly controlled by drugs, new surgical methods are being developed. One recent accomplishment has been the use by an NEI grantee of an enzyme to effect a type of "chemical surgery" by severing certain nerve pathways to the eye and thus enhancing the effect of drugs in lowering the intraocular pressure in galucoma patients who could not be helped by any other means.

DIABETIC RETINOPATHY

Mr. CONTE. Would you explain what diabetic retinopathy is? What is the link between diabetes and eye disease?

Dr. KUPFER. One of the leading causes of blindness in the United States, diabetic retinopathy is the primary ocular complication of diabetes and is responsible for approximately 10 percent of all new blindness reported each year in this country. Among those 45 to 74 years of age, the disease accounts for about 20 percent of all new blindness.

Although the immediate cause of diabetic retinopathy is unknown, the condition seems to involve progressive impairment of the retaina's blood circulation. Visual loss resulting from diabetic retinopathy may be associated with a number of causes including bleeding into the vitreous, the clear, jelly-like substance which fills the center of the eye, formation of scar tissue, or detachment of the retina. All of these conditions are usually preceded by growth of newly formed blood vessels along the internal surface of the retina. It is from these vessels that hemorrhages into the vitreous occur, and it is at the site of new vessels that scar tissue forms. Subsequent shrinkage of the scar tissue and of the vitreous, to which the new vessels adhere, is the immediate cause of retinal detachment.

While the use of insulin and proper attention to diet have improved the well-being and life expectancy of diabetes patients, some of the complications associated with diabetes have increased. In general, the incidence and severity of diabetic retinopathy are proportional to the duration of diabetes. Of patients who suffer from diabetes for 10 years, 50 percent show some degree of retinopathy; of those suffering for 15 years, 75 percent show some degree; and of those with diabetes for 25 years, 95 percent show signs of retinopathy.

SCIENTIST-TO-PHYSICIAN COMMUNICATION

Mr. CONTE. Would you tell me what special efforts you intend to undertake this year to disseminate research findings to the health care delivery system?

Dr. KUPFER. In the area of scientist-to-physician communication, NEI has engaged in a number of ad hoc activities. One of the Institute's earliest efforts in the field was an exhibit, "The Physician

and the Prevention of Visual Disability" presented at the 1971 meeting of the American Medical Association and New York Medical Society. The exhibit encouraged glaucoma and amblyopia screening by the nonophthalmic primary physicians.

More recently, Institute staff helped prepare a publication for physicians who treat diabetes patients. The booklet, designed in conjunction with the Institute-supported diabetic retinopathy study (DRS), explains the DRS in great detail and encourages the primary physician to refer diabetes patients with retinopathy to clinics participating in this nationwide clinical trial of photocoagulation.

Another example of scientist-to-physician communication was an in-depth interview conducted by the American Optometric Association News and published in their April 1974 issue. The lengthy article explained not only the research objectives and philosophies of the Institute, but also called for greater cooperation between the NEI and the optometric research community.

Several months ago, the NEI Clinical Director was interviewed by a reporter from the Physicians Radio Network on the Institute's research activities and its clinical program.

The most recent activity in the scientist-to-physician area is an NEI program exhibit which was presented at the October 1974 meeting of the American Academy of Ophthalmology and Otolaryngology. The exhibit presents the five major NEI program areas—retinal and choroidal diseases glaucoma, cataract, corneal diseases, and sensorymotor disorders—and is clinically oriented so that it will have strong appeal to the practicing ophthalmologist. Its objective is to demonstrate to the clinician how NEI-supported research is helping to provide new tools for the improved prevention, diagnosis, and treatment of eye disorders.

During the coming year, additional efforts of this type will be continued and expanded if staff is made available.

BUDGET ADEQUACY

Mr. Conte. Do you believe that this budget is adequate to meet your responsibilities?

Dr. Kupfer. In the fiscal year 1976 budget, the National Eye Institute will receive $3,811,000 for its highest priority new research grants. At the same time, noncompeting grants of a lower order of priority will be terminated. Thus, despite these severe reductions, we will be able to fund at least a portion of new and competing grants to maintain some of the momentum generated in the vision research field.

TUMORS OF THE CORNEA AND CONJUNCTIVA

Mr. Conte. Would you tell me about your planned research into the role of viruses in causing tumors of the cornea and conjunctiva?

Dr. Kupfer. Tumors of the cornea and conjunctiva are uncommon but, because of their seriousness, important conditions. These conditions have been studied incompletely in the past as a result of their relative infrequency and lack of promising areas for investigation. The latter situation has been changed, however, by the emerging awareness of the possible role of viruses in causing some forms of cancer

and by recognition of the probable role of immunologic mechanisms in the development and spread of tumors. These disorders deserve reappraisal in consideration of current concepts and techniques of cancer research.

External ocular tumors of the eyelid skin are much more common. Environmental factors are probably important in at least some of these disorders. Reevaluation of these tumors with attention to current methods of prevention, diagnosis, and treatment indicates that more research is needed in this area.

Research in this area is highlighted in the new report on vision research program planning and is considered a priority area in vision research which will be emphasized over the next few years. We expect that additional scientists will become interested in research on tumors of the cornea and conjunctiva as well as of other parts of the eye.

SENILE CATARACTS

Mr. CONTE. Why are cataracts associated with aging? What is the link?

Dr. KUPFER. The most common form of cataract is related to normal aging of the eye. This is sometimes referred to as senile cataract. The lens, which is composed of cells that form transparent protein fibers, continues to grow slowly throughout life. Over a period of time the fibers become more compacted in the center of the lens, and begin to lose their transparency. The National Eye Institute is supporting a number of studies related to senile cataracts.

Researchers supported by grants from the National Eye Institute have studied the effect of aging on protein synthesis and protein structure of the lens and have correlated these findings with the development of geriatric cataract. It has been demonstrated that the alpha-crystallin macromolecules of the lens increases in size as a function of aging. The only chemical difference noted between the large macromolecules and normal sized alpha-crystallin is the presence of 2–3 percent sugar and a decrease in solubility. These findings suggest that the aggregation of the alpha-crystallin as a function of aging may be associated with the development of geriatric cataracts.

PROGRAMS WARRANTING INCREASED SUPPORT

Mr. CONTE. Would you tell us in which of your five major programs the study of the National Advisory Council felt that increased support has warranted?

Dr. KUPFER. The study conducted by the NAEC identified specific areas in each of our five major program areas as deserving additional support. They are as follows:

RETINAL AND CHOROIDAL DISEASES

Pigment epithelium research, because of the basic relationship of this tissue to retinal function, and because it is extremely important in understanding a number of visual disorders such as retinitis pigmentosa, macular degeneration, and retinal detachment; studies or retinal

organization and information processing particularly in primates with systems likely to be comparable to those of man; investigations of retinal pigmentary malfunctions and retinal storage diseases, encompassing a detailed study of retinal biochemistry; retinal and choroidal blood circulation research because of its relevance to diabetic retinopathy, macular degeneration, and other major disease entities, and because of the availability of new research techniques; the development of practicable animal models for inflammatory diseases of the choroid and retina; correlations between disease pictures observed in the clinic and the histologic, biochemical, and physiologic manifestatations of those diseases; clinical research related to retinal and choroidal diseases, with emphasis on research protocols, precise measurements, and the selective use of controlled, randomized clinical trials for evaluating existing therapeutic regimes and for appraising the efficacy of new methods of therapy, and in view of the genetic aspects of retinoblastoma, the discovery of intraocular enzyme abnormalities in eyes with this tumor and the emerging role of immunologic procedures for tumor diagnosis and assessment of prognosis, research on tumors of the retina and choroid.

CORNEAL DISEASES

Tissue culture, with appropriate biochemical analysis, of abnormal human corneal tissue removed at the time of corneal transplantation; the encouragement of immunologists to become involved in corneal research and to address major problems related to disease and graft systems; additional controlled clinical trials of new antiviral drugs useful in treating herpes simplex and other important infective diseases; the possible role of viruses in the causation of neoplasms affecting the cornea and conjunctiva.

CATARACT

Investigations of the biochemical and biophysical processes involved in the maintenance of normal lens hydration, particularly in primates and human beings, to determine how aberrations in these mechanisms lead to lens opacification; studies of protein changes in the lens and the role of protein aggregation in the development of cataracts; the search for new animal models for studying congenital cataracts and for investigating the degenerative processes associated with aging and cataract production; the organization of controlled, randomized clinical trials to evaluate alternate methods for optical rehabilitation.

GLAUCOMA

Studies of the mechanism of pressure-induced visual function damage in the primate and in man; investigations on the mechanisms of aqueous production and outflow in primates and man; controlled randomized clinical trials of medical and surgical therapy for open-angle glaucoma; research designed to predict, with increasing accuracy, the risk of a person to closed-angle glaucoma.

Further studies of strabismus and amblyopia, especially in primates, and other useful experimental models of these disorders; physiologic, neurochemical, and pharmacologic studies of oculomotor control, particularly in monkeys; research leading to the prevention of degenerative, high myopia and to the prevention of the changes associated with this condition that may endanger sight; research on neural mechanisms in the sensory system, and the correlation of these mechanisms with psychophysical functions and the processes of vision, directed toward the maximization of residual visual function following disease of the visual pathways.

Mr. CONTE. Thank you.

Mr. FLOOD. Thank you, Dr. Kupfer, for a very exciting visit.

Dr. KUPFER. Thank you, sir.

Justification of the Budget Estimates

Appropriation Estimate

NATIONAL EYE INSTITUTE

For expenses necessary to carry out Title IV, parts F and I of the Public Health Service Act, with respect to eye diseases and visual disorders, [$44,133,000] *$39,201,000.*

For the "National Eye Institute" for the period July 1, 1976, through September 30, 1976, $9,800,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation

	1975 Estimate 1/	1976 Estimate
Appropriation	$44,133,000	$39,201,000
Comparative transfer to:		
"Research Resources" (For Rhesus Monkey Supply Program)	-76,000	---
"Office of the Director" (For transfer of the institutional relations branch from the Division of Research Grants, NIH Management Fund)	-17,000	---
Total, obligations	$44,040,000	$39,201,000

1/ Excludes 1973 restorations in the amount of $15,000.

Summary of Changes

1975 Estimated Obligations	$44,040,000
1976 Estimated Obligations	39,201,000
Net Change	-$ 4,839,000

	1975 Pos.	1975 Amount	Change Pos.	Change Amount
Increases:				
A. Built-in				
1. Within-grade salary increase	--	--	--	+ 45,000
2. Extra day of pay	--	--	--	+ 13,000
3. FTS rate increase	--	--	--	+ 5,000
4. Bureau of employees compensation	--	--	--	+ 1,000
5. Increased cost of postage	--	--	--	+ 1,000
6. Payment to NIH Management Fund	--	--	--	+123,000
Subtotal	--	--	--	+188,000
B. Program:				
1. Research grants				
a. Noncompeting continuations	--	7,640,000	--	+11,320,000
b. Competing (New continuations and supplementals)	--	11,320,000	--	+ 3,811,000
2. Fellowships:				
a. Noncompeting continuations	--	160,000	--	+ 1,852,000
b. Competing (new continuations and supplementals)	--	2,493,000	--	+ 641,000
Total increases	--	---		+17,812,000
Decreases:				
A. Program:				
1. Research grants:				
a. Noncompeting completed or converted to competing status	--	17,640,000	--	- 9,479,000
b. Competing completed or converted to noncompeting	--	11,320,000	--	-11,320,000
2. Fellowships:				
a. Noncompeting completed or converted to competing status	--	---	--	---
b. Competing completed or converted to noncompeting	--	2,493,000	--	- 1,852,000
Total decreases	--	---	--	-22,651,000
Total, Net Change	--	---	--	- 4,839,000

Explanation of Changes

Increases:

A. Built-in: These increases provide; (1) $45,000 for within-grade salary increases. $25,000 for Intramural Laboratory and Clinical Research and $20,000 for Research Management and Program Services. (2) $13,000 for an extra day of pay, $7,000 for Intramural Laboratory and Clinical research and $6,000 for Research Management and Program Services. (3) (4) (5) $5,000 for increased costs for using the Federal Tele-communicative System; $1,000 for an increase in payment to the Bureau of Employees Compensation; $1,000 for increased cost of postage, all of which are included in RMPS; and (6) $123,000 for increased costs associated with the NIH Management Fund for centrally furnished services in the Intramural Laboratory and Clinical Research Program.

B. Program:
   1. Research grants:
      a. The increase of $11,320,000 in noncompeting research grants represent the continuation of previsouly awarded grants plus "new" continuations resulting from grants made in 1975.

      b. The amount of $3,811,000 in competing research grants reflects: (1) $1,211,000 for 20 new awards; (2) $2,550,000 for 36 competing continuations; and (3) $50,000 in supplementals.

   2. Fellowships:
      a. The Increase of $1,852,000 in noncompeting fellowships represent the continuation of previously awarded fellowships in 1975. The number of continuations increased by 123 from 11 in 1975 to 134 in 1976

      b. The amount of $641,000 in competing fellowships reflects an increase for 4 new awards.

Decreases:

A. Program:
   1. Research grants:
      a. The decrease of $9,479,000 is broken as follows: $2,793,000 represents 56 noncompeting regular research grants that were completed in 1975 or that are being converted to competing status in 1976, and $6,686,000 represents a reduction in lower priority continuation costs.

      b. The decrease of $11,320,000 reflects the completion or conversion of 173 competing grants to a noncompeting status.

   2. Fellowships:
      a. The decrease of $1,852,000 reflects the completion or conversion of 123 competing fellowships to a noncompeting status.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
152	Retinal and Choroidal Diseases	--	$14,016,000	--	$12,031,000	--	-$1,985,000
154	Corneal Diseases	--	6,596,000	--	5,202,000	--	- 1,394,000
156	Cataract	--	3,445,000	--	3,189,000	--	- 256,000
158	Glaucoma	--	5,012,000	--	4,892,000	--	- 120,000
160	Sensory-Motor Disorders and Rehabilitation	--	7,459,000	--	6,247,000	--	- 1,212,000
162	Intramural Laboratory and Clinical Research	84	4,900,000	76	5,028,000	-8	+ 128,000
164	Research Management and Program Services	58	2,612,000	56	2,612,000	-2	--
	Total obligations	142	$44,040,000	132	$39,201,000	-10	-$4,839,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	142	132	- 10
Full-time equivalent of all other positions	6	6	--
Average number of all employees	137	127	-10
Personnel compensation:			
Permanent positions	$ 2,143,000	$ 2,392,000	+$ 249,000
Positions other than permanent	120,000	188,000	+ 68,000
Other personnel compensation	40,000	80,000	+ 40,000
Subtotal, personnel compensation	2,303,000	2,660,000	+ 357,000
Personnel benefits	270,000	313,000	+ 43,000
Travel and transportation of persons	160,000	90,000	- 70,000
Transportation of things	10,000	4,000	- 6,000
Rent, communications and utilities	95,000	139,000	+ 44,000
Printing and reproduction	44,000	60,000	+ 16,000
Other Services:			
Project contracts	2,322,000	2,322,000	--
Payment to NIH Management Fund.	2,827,000	2,950,000	+ 123,000
Other	1,010,000	609,000	- 401,000
Supplies and materials	362,000	317,000	- 45,000
Equipment	431,000	498,000	+ 67,000
Grants, subsidies and contributions	34,206,000	29,239,000	- 4,967,000
Total, obligations by object	$44,040,000	$39,201,000	-$4,839,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1975 Senate Report	
1. The Committee understands that there is research underway to dissolve cataracts through chemicals rather than resorting to surgery; and feels that this research should be strongly supported. (Page 62)	1. The Laboratory of Vision Research scientists have uncovered the basic mechanisms that are involved in cataracts associated with diabetes and galactosemia, so it is now possible, in animals to delay the onset of these cataracts with chemical agents. Increased funding will allow for research in follow-up experiments for effecting delay or prevention of cataracts based on the past few years developments.
2. The Committee intends that part of the additional resources being made available to the Institute be used to implement information dissemination to practitioners and the public. (Page 63)	2. 73,400 NEI publications were distributed to the public and to practitioners during the year. The publications furnished information on: Cataract, Diabetic Retinopathy, Retinitis Pigmentosa, Macular Degeneration, Statistics on Blindness, Corneal Disease, Blindness and Services to the Blind in the U. S. Retinal Detachment, Refractive Errors and Glaucoma.
3. The Committee recommends that a portion of the Congressional increases be used to expand research in macular degeneration. (Page 63)	3. Experimental models for macular degeneration in the rhesus monkey have been developed. Increased funding will allow for the stimulation of research in the role of retinal and choroidal circulation in diabetic retinopathy and macular degeneration.
4. The Committee was most interested in reports of a new surgical procedure, vitrectomy developed with NEI support, which has demonstrated its usefulness in restoring sight to patients who have lost vision from diabetic retinopathy. However, the Committee is concerned that adequate clinical evaluation of the safety and efficacy of this new therapy be undertaken as soon as possible to assure maximum benefit and minimum risk to patients. (Page 63)	4. The NEI will coordinate a large-scale clinical trial in vitrectomy, to evaluate this technique that holds great promise as a treatment for diabetic retinopathy and other eye diseases. It is anticipated that this study will begin in 1975.

AUTHORIZING LEGISLATION

Legislation	1976 Authorized	1976 Appropriation Requested
Public Health Service Act Section 301 -- Research and Investigations in General.....	Indefinite	
Title IV, Part F -- National Eye Institute.....	Indefinite	$34,554,000 2/
Title IV, Part I -- National Research Service Award Act.....	1/	4,647,000 2/

1/ Authorization expires June 30, 1975, extension legislation is proposed.

2/ Funding estimate only.

National Eye Institute

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1970	$22,073,000	$22,073,000	$23,330,000	$22,652,000
1971	24,325,000	29,217,000	29,217,000	29,435,000
1972	31,258,000	34,437,000	38,404,000	35,670,000
1973	33,797,000	36,809,000	43,247,000	36,809,000 1/
1974	32,092,000	36,631,000	46,631,000	39,998,000 2/
1975	39,947,000	38,878,000 3/	50,000,000	44,040,000
1976	39,201,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes Research and Development contracts not considered by House due to lack of authorizing legislation.

National Eye Institute

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1970	$23,685,000	$23,685,000	$25,000,000	$24,342,500
1971	25,686,000	30,986,000	30,986,000	30,032,000
1972	32,639,000	36,022,000	40,187,000	37,132,500
1973	37,384,000	38,562,000	45,000,000	38,562,000 1/
1974	32,092,000	36,631,000	46,631,000	41,177,000 2/
1975	39,947,000	38,878,000 3/	50,000,000	44,133,000
1976	39,201,000			

1/Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/Appropriation after reduction.

3/Excludes Research and Development contracts not considered by House due to lack of authorizing legislation.

Justification
National Eye Institute

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	142	$ 2,573,000	132	$ 2,973,000	-10	+ 400,000
Other expenses.....	--	41,467,000	--	36,228,000	--	-5,239,000
Total.....	142	$44,040,000	132	$39,201,000	-10	-$4,839,000

General Statement

For the people of the United States, preservation and restoration of vision requires coordinated programs of research, education, and patient care. These interrelated programs must provide for research and research training in the basic and clinical sciences related to vision, education in the basic biological and applied clinical disciplines pertaining to the eye and associated structures, and health care for patients with vision disorders and eye diseases.

As the principal national resource for support of research in the prevention, diagnosis, and treatment of diseases of the eye and the visual system, the National Eye Institute is reponsible for promoting and coordinating, on a continuing basis, a nationwide vision research program. Research activities supported by the Institute are currently grouped under five major research programs: Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma, and Sensory-Motor Disorders and Rehabilitation.

The eye and its connections with the brain constitute man's most highly developed sensory system. It not only provides detailed visual images which are essential for mobility and the fulfillment of basic needs, but is man's most important source of information for coping with the intricacies of a modern technological society. In a world where printed words and televised images convey knowledge, where transportation systems are mechanized and complex, and a myriad of instruments and tools are required for the performance of many complicated tasks, good vision is of primary importance, and with the single exception of cancer, Americans have indicated that they fear blindness more than any other physical affliction.

Although steady progress has been made in the field of visual rehabilitation, and many ingenious mechanical and electronic aids for the visually handicapped have been developed, science has not been able to develop a satisfactory substitute for the versatility and capacity of the human visual system, nor is it likely to do so in the near future.

While work in rehabilitation must continue, a more immediate goal is the preservation of vision through development of improved methods of prevention, diagnosis, and treatment of eye diseases. The eye and visual system are susceptible to a multitude of disorders. These vary considerably in effect and seriousness. Eye conditions may be localized to one part of the eye or

have multiple effects. They strike young and old, and may range in severity from temporary irritations or easily correctable optical errors to devastating infections and degenerative disorders.

In the United States, estimates of the number of people classified as "legally" blind range from 350,000 to 500,000. Such a classification is necessary for determining eligibility for special benefits from public and private agencies which afford those with severe visual handicaps some measure of financial relief. Yet these numbers greatly understate the problem of visual disability, for there are at least 10 million people--1 out of every 20--who suffer from significant, uncorrectable impairment of vision. Estimates of annual income lost due to blindness range from $600 million to $1 billion. The estimated cost to public and welfare agencies for services to blind people is over $500 million. The costs resulting from severe visual disability short of blindness are unknown but surely are great.

Research offers the only hope for reducing the enormous personal and social costs of eye disorders. Through studies in the laboratory and clinic, great strides already have been made toward this end. The above statistics would be even higher but for the many accomplishments during the past two decades in such fields as cataract surgery, glaucoma therapy, and treatment of bacterial ulcers of the cornea. Yet these diseases remain leading causes of blindness and visual disability and for other major problems, there is no effective means of prevention, cure, or control.

The great toll taken each year in the United States by eye diseases is not measured in terms of mortality, for few disorders originating in the eye cause death--but rather in degrees of physical limitation and financial burden. However such measurements are inadequate, for they cannot convey the hardship nor the mental anguish of having to function in a complex environment deprived of normal vision.

In November 1974, the National Eye Institute convened a special Committee of the National Advisory Eye Council to develop recommendations for future vision research program development. The Committee's recently completed report represents the first attempt to develop such guidelines.

This document focuses attention on the most crucial problems now facing scientists working in vision research as well as on the most promising opportunities for further advancement. Recommendations for the future development of vision research support are not intended to be implemented as a Federal plan which would be imposed upon, and stifle the creativity of, a highly productive and innovative research community. Rather, the intent is to present a comprehensive overview of the present status of vision research in the United States today and discuss major needs and research leads which have a high probability of being exploited for significant gain. The ultimate aim of this report is to provide structure and general guidance for the development of vision research over the next few years in order to concentrate resources on solving problems which will lead to the improved prevention, diagnosis, and treatment of eye and visual system disorders. In future years this report will be updated and progress toward achieving the objectives it contains will be documented.

In recent years, advances in vision research supported by the NEI have made significant inroads against visual disability and blindness. These have led to a shortening of hospitalization, a shift from inpatient to outpatient treatment, and a reduction in the costs of vocational rehabilitation or lifetime support. Some highlights are: Cataract surgery has been made safer, easier, and more successful through several technical improvements made possible by NEI support; (2) recent research advances suggest that the NEI is on the threshold of a scientific breakthrough that will allow cataracts to be prevented medically and make possible great savings in hospitalization and surgical costs; (3)

scientific findings which appear to point the way to improved medical care in glaucoma through early detection before loss of sight occurs; (4) the development of vitrectomy is one of the most exciting new fields of eye surgery, with a significant potential for restoring sight to people blind from certain kinds of retinal and vitreous disease; and (5) the use of soft contact lenses as an aid to healing and relief of pain in corneal diseases has revolutionized the treatment of this significant cause of disability and lost productivity.

As the prevalence of eye diseases such as trachoma has greatly diminished in the United States (though trachoma remains the leading cause of blindness in underdeveloped countries), the importance of the chronic eye diseases associated with aging--retinal degeneration, cataract, and glaucoma--has dramatically increased. In addition, the improved survival of people with diabetes has led to a greatly increased incidence of visual disability and blindness from diabetic retinopathy, a retinal disorder usually associated with long duration of diabetes.

In FY 1976, continued emphasis will be placed on the support of quality laboratory research, application of epidemiological techniques to eye disease problems, and stimulation of additional clinical research, particularly in retinal and choroidal diseases, which will help provide the scientific base upon which more effective vision care and eye disease prevention programs can be built. In this manner, the National Eye Institute approaches its goal of reducing the enormous toll in human suffering and economic loss taken each year in our nation by blindness and visual disability.

DHEW - National Institutes of Health

Crosswalk - 1975 Column 1976 President's Budget

INSTITUTE: National Eye Institute

Mechanism / Program	Research Grants						Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials		Training Programs					
	Non-Competing	Competing	Multi-disciplinary Center	Other	Grants	Fellowships				
Retinal & Choroidal Diseases	5,856	4,822		215	585	938		1,600		14,016
Corneal Diseases	3,369	1,998		97	386	446		300		6,596
Cataract	1,923	1,116		45	191	170		---		3,445
Glaucoma	1,923	1,788		61	439	379		422		5,012
Sensory-motor & Rehabilitation	4,569	1,596		181	393	720		---		7,459
Intramural Laboratory & Clinical Research							4,900			4,900
Research Management & Program Services									2,612	2,612
Total Obligations	17,640	11,320		599	1,994	2,653	4,900	2,322	2,612	44,040

DHEW - National Institutes of Health

Crosswalk - 1976 Column 1976 President's Budget

INSTITUTE: National Eye Institute

Program \ Mechanism	Research Grants									
	Regular Program		Specials		Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
Retinal & Choroidal Diseases	6,765	1,235		193	682	944		2,212		12,031
Corneal Diseases	3,579	743		---	409	446		25		5,202
Cataract	2,337	385		75	222	170		---		3,189
Glaucoma	3,317	850		25	238	377		85		4,892
Sensory-motor & Rehabilitation	4,315	598		175	443	716		---		6,247
Intramural Laboratory & Clinical Research							5,028			5,028
Research Management & Program Services									2,612	2,612
Total Obligations	20,313	3,811		468	1,994	2,653	5,028	2,322	2,612	39,201

National Eye Institute

Budget Mechanism

	1975* Number	1975* FTE[1/]	1975* Amount	1976 Number	1976 FTE[1/]	1976 Amount
Grants						
Regular						
Non-competing	303		$17,640,000	332		$20,313,000
Competing	83		5,410,000	36		2,550,000
New	90		5,860,000	20		1,211,000
Supplemental	(4)		50,000	(4)		50,000
Subtotal	476		28,960,000	388		24,124,000
Special						
Research career program	19		529,000	15		375,000
Scientific evaluation	--		70,000	--		93,000
Subtotal	19		599,000	15		468,000
Total Grants	495		29,559,000	403		24,592,000
Fellowships						
Non-competing	11	11	160,000	134	134	2,012,000
Competing	--	--	--	--	--	--
New	166	166	2,493,000	--	--	641,000
Supplemental	--	--	--	--	--	--
Subtotal	176	176	2,653,000	134	134	2,653,000
Training Grants						
Non-competing	30	81	1,994,000	19	51	1,994,000
Competing	--	--	--	--	--	--
New	--	--	--	--	--	--
Supplemental	--	--	--	--	--	--
Subtotal	30	81	1,994,000	19	51	1,994,000
Laboratory and Clinical Research			4,900,000			5,028,000
Research and Development Contracts			2,322,000			2,322,000
Biometry, Epidemiology & Field Studies			487,000			487,000
Research Management & Program Services			2,125,000			2,125,000
Total			$44,040,000			$39,201,000

1/ Full-time equivalents.

*Excludes 1973 appropriation restorations.

Retinal and Choroidal Diseases

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....		$14,016,000		$12,031,000		-$1,985,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	100	5,856,000	130	6,765,000	+30	+ 909,000
Competing.....	74	4,822,000	18	1,235,000	-56	- 3,587,000
Special.....	5	215,000	4	193,000	- 1	- 22,000
Subtotal.....	179	10,893,000	152	8,193,000	-27	- 2,700,000
Fellowships.....	62	938,000	63	944,000	- 1	+ 6,000
Training Grants.....	30	585,000	17	682,000	-13	+ 97,000
Research & Development Contracts.....	23	1,600,000	27	2,212,000	+ 4	+ 612,000
Total.....		$14,016,000		$12,031,000		-$1,985,000

NOTE: Numbers for training grants reflect full-time equivalents.

Introduction

Retinal and choroidal diseases account for more blindness in the United States than any other visual disorders. The retina is the light-sensitive tissue at the back of the eye, and the choroid is the underlying, blood vessel-rich layer responsible for retinal nourishment. These structures are the primary sensory and vascular tissues of the eye and are closely related. As a result of their interdependencies, they are subject to systemic influences as well as to ones peculiar to the eye.

More than 147,000 American are blind as a result of retina and choroidal diseases, and an estimated 15,000 additional people become blind each year from these disorders. Of all the severe diseases which can affect these tissues, macular degeneration (a deterioration of the small area of the retina responsible for sharp vision) and diabetic retinopathy (a progressive disorder in the blood vessels of the retina associated with long duration of diabetes) are among the most common causes of blindness.

Unfortunately, there is no known cure or available means of preventing retinal and choroidal diseases. Early diagnosis is a problem because of the relative inaccessability of the retina and choroid and the similar appearance of many diseases affecting these tissues. Except in cases of retinal detachment, which often can be surgically repaired, progress against this group of diseases has been severely impeded by the paucity of knowledge of the fundamental

processes which underlie normal retinal function.

Program Plans for 1976

Opportunities for new and promising investigations are present, and increased research is needed to build the foundation of basic scientific knowledge and to establish the basis for improvements in the prevention, diagnosis, and treatment of retinal and choroidal diseases. Therefore, research in the following areas will be stimulated: (1) pigment epithelium because of the basic relationship of this tissue to normal and abnormal retinal function and the recent development of new techniques for basic science and clinical investigation; (2) studies of the organizational structure of the retina and how it processes visual information, particularly in primates with systems comparable to man; (3) studies of retinal pigmentary disorders and retinal storage diseases encompassing a detailed study of retinal biochemistry; (4) the role of retinal and choroidal circulation in diabetic retinopathy and macular degeneration; (5) development of animal models for inflammatory diseases of the choroid and retina; (6) clinical correlations with histologic, biochemical, and physiological abnormalities observed in the retina and choroid; and (7) clinical research related to retinal and choroidal diseases. Clinical investigations are essential for the evaluation of existing treatments and appraising the effectiveness of new methods of therapy.

Accomplishments for 1975

Research in this program involves a broad base of scientific inquiry, disciplines and methodology. The objectives are to develop the foundation of scientific knowledge and to establish the basis for improvement in the prevention, diagnosis and treatment of retinal and choroidal diseases in man. During 1975, progress in research against retinal and choroidal diseases has been made in the following areas: (1) refinement of techniques which allow surgeons to simultaneously cut vitreous fibers, remove them from the eye, and replace the vitreous with a balanced salt solution, a procedure which has proven successful in treating patients who previously had been considered hopelessly blind from diseases such as diabetic retinopathy; (2) development of methods of studying a variety of conditions of retinal toxicity and degeneration in which retinal blood flow is an important factor; (3) design of studies to analyze the efficiency of argon laser burns in blood vessel closure or obliteration, and factors relating to the movement of fluid between various retinal and choroidal components; (4) improved understanding of the biological role of hyaluronic acid in the vitreous which may lead to the possible use of this biopolymer in control of inflammation and regenerative processes; (5) greater awareness of the critical role of the pigment epithelium, the outermost retinal layer, in retinal degenerative diseases; (6) improved understanding of the structure of photoreceptor membranes and visual pigment properties; (7) development of experimental models for macular degeneration in the rhesus monkey; and (8) improvements of ultrasonic diagnostic systems to ensure a more reliable diagnosis of ocular and orbital tumors.

Corneal Diseases

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....		$6,596,000		$5,202,000		-$1,394,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	51	3,369,000	45	3,579,000	- 6 +	210,000
Competing.....	27	1,998,000	11	743,000	-16 -	1,255,000
Special.....	4	97,000	--	--	- 4 -	97,000
Subtotal.....	82	5,464,000	56	4,322,000	-26 -	1,142,000
Fellowships.....	30	446,000	30	446,000	--	--
Training Grants.....	11	386,000	10	409,000	- 1 +	23,000
Research & Development Contracts.....	2	300,000	1	25,000	- 1 -	275,000
Total.....		$6,596,000		$5,202,000		-$1,394,000

NOTE: Numbers for training grants reflect full-time equivalents.

Introduction

The cornea, the transparent protective layer at the front of the eye, can become clouded or scarred from disease and injury. Diseases affecting the cornea include those caused by infectious agents such as bacteria and viruses, congential and developmental influences, and degenerative processes. The cornea is more vulnerable than any other part of the eye to accidental injury. Because it is one of the major components of the eye's focusing system, irregular curvature of the cornea, responsible for astigmatism, is a common refractive error.

There are an estimated 21,000 Americans blind from corneal diseases, accounting for about 6% of all blindness in the country. Many more individuals, though not legally blind, have varying degrees of visual impairment because of corneal diseases. These disorders have great impact not only in reducing visual acuity but also in causing suffering, for they are the most painful of eye disorders.

Program Plans for 1976

Research related to corneal diseases--including disorders of the conjunctiva and the tear glands will receive added attention.

Major needs and opportunities in corneal diseases research to be emphasized are: (1) tissue culture and biomedical analysis of diseased human corneal

tissue removed at the time of corneal transplantation; (2) encouragement of immunologists to become involved in corneal research and to address major problems related to disease and corneal transplantation including the rejection of corneal grafts; (3) additional controlled clinical trials of new antiviral drugs useful in treating herpes simplex and other important infective diseases of the cornea; and (4) the possible role of viruses in causing tumors of the cornea and conjunctiva.

Accomplishments for 1975

The transport of sodium, chloride, and other ions across the cornea has been studied in order to clarify how its thin layers of cells (epithelium and endothelium) regulate the amount of water in the cornea. The influences of some chemicals and reagents have been determined and various agents capable of modifying permeability and transport have been evaluated. This work has resulted in better understanding of the body's normal mechanisms for keeping the cornea transparent. Infection of the cornea by herpes simplex virus is one of the most important ocular diseases. An antiviral drug (adenine arabinoside) has been found very effective against this disease when applied topically.

Another development stemming from basic research is a new medium which allows longer storage of corneas before tranplantation. Several thousand corneal transplants are done in the United States each year, and a prolongation of cornea storage time from a few hours to five or six days facilitates the management of cornea transplantation.

The soft contact lens has proven useful in treating many kinds of corneal disease. In some aged individuals and in some patients with arthritis, normal tear production becomes deficient and the eye dries and becomes scarred. Soft lenses have been shown to provide a moist protective blanket for such eyes. Also, by protecting the surface of the cornea they have permitted corneal ulcers to heal, and by creating a smooth surface after injuries and other conditions which create irregularities in the corneal surface they have prevented tissue damage. In these treatments the soft lenses still permit good vision since their smooth spherical surface becomes the effective front surface of the eye.

The use of long-acting antibiotic drugs to prevent secondary infections in trachoma is a significant new chemotherapeutic approach for the treatment of this important public health problem in many parts of the world. A substantial number of trachoma cases have been treated in North Africa, particularly in some areas around Tunis.

Cataract

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$3,445,000		$3,189,000		-$256,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	35	1,923,000	39	2,337,000	+4	+ 414,000
Competing	13	1,116,000	6	385,000	-7	- 731,000
Special	2	45,000	3	75,000	+1	+ 30,000
Subtotal	50	3,084,000	48	2,797,000	-2	- 287,000
Fellowships	12	170,000	11	170,000	-1	--
Training Grants	5	191,000	6	222,000	+1	+ 31,000
Research & Development Contracts	--	--	--	--	--	--
Total		$3,445,000		$3,189,000		-$256,000

NOTE: Numbers for training grants reflect full-time equivalents.

Introduction

Cataract, another leading cause of blindness and visual disability in the United States, is a cloudiness or opacity in the normally clear lens of the eye which obstructs vision by interfering with the passage of light rays to the retina. In most cases the cause of cataract cannot be determined, but the most common form of the disease is related to the aging process in the eye.

Thus, of the estimated 3,013,000 people in the United States who have cataract, 2,212,000 are 65 years of age and older, and 565,000 are 45 to 64 years of age. In addition, more than 45,000 persons are legally blind because of cataract.

Cataract removal is one of the most successful major surgical procedures performed today. Yet, due to psychological, social, economical, and other factors, cataract remains a leading cause of blindness. Approximately 400,000 cataract extractions are performed annually at an estimated cost of about $1 billion. Cataract, therefore, has not only a tremendous physical impact but a financial one as well on thousands of people. Furthermore, cataract surgery involves removing the natural lens of the eye, and a substitute--either in the form of a thick eyeglass, contact lens, or an intraocular plastic lens--must be provided. Although many patients find it difficult to adjust to the loss of side vision and magnification of image size which are the consequences of spectacle lenses, satisfactory visual acuity may be restored. Discovering means of preventing cataract, and thus alleviating the disability, finanical

burden, lost productivity, and human suffering associated with this disorder, is a high priority goal of vision research.

Program Plans for 1976

Opportunities for research related to cataract stem from new ideas concerning how the lens remains clear and why it becomes cloudy, the availability of a variety of animal models, and the availability of human lenses for research. Therefore, major needs and opportunities in cataract research to be stressed are: (1) the mechanisms which lead to lens opacification, investigations of the biochemical and biophysical processes operative in the maintenance of normal lens hydration, particularly in primates and human beings; (2) the study of protein changes in the lens and the role of protein aggregation in the development of cataracts; and (3) the search for new animal models for studying congenital cataracts and for investigating the degenerative processes associated with aging and cataract production.

Accomplishments for 1975

Aggregation of proteins in the lens leads to loss of lens transparency because of the scattering of light by these clumps. The structure of these proteins has been further elucidated, indicating that they have a high molecular weight and a characteristic way in which their subunits are organized. Because these studies were conducted on solutions separated biochemically from the lens, it was desirable to discover whether or not such aggregates can be detected within the intact lens. A method has been devised in which the size of proteins in the intact lens can be measured optically. This discovery now opens the door to a series of investigations of the state of proteins in normal and various types of cataractous lens without removing them from the body.

Cataracts are sometimes found in children in the presence of low sugar (hypoglycemia). It has been possible to recreate this condition in the laboratory using mouse lens. An enzyme having an unusual sensitivity to glucose concentration has also been discovered. This finding indicates that an enzyme may be responsible for the development of such types of cataract in children.

Another important finding is that sunlight may be a factor in some cases for early changes in the lens. Although the idea that exposure to sunlight may play a role in the formation of a type of cataract had been postulated a long time ago, only recently has it been possible to demonstrate experimentally that an alteration actually occurs in the protein of the lens.

Glaucoma

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$5,012,000		$4,892,000		-$ 120,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	31	1,923,000	30	3,317,000	-1	+ 1,394,000
Competing	12	1,788,000	12	850,000	--	- 938,000
Special	2	61,000	1	25,000	-1	- 36,000
Subtotal	45	3,772,000	43	4,192,000	-2	+ 420,000
Fellowships	24	379,000	25	377,000	+1	- 2,000
Training Grants	8	439,000	6	238,000	-2	- 201,000
Research & Development Contracts	5	422,000	1	85,000	-4	- 337,000
Total		$5,012,000		$4,892,000		-$ 120,000

NOTE: Numbers for training grants reflect full-time equivalents.

Introduction

Glaucoma, one of the leading causes of blindness in this country, is actually a group of diseases characterized by elevated pressure within the eye and loss of visual function. The pressure within the eye is directly related to the status of the aqueous humor which is continually being produced and exuded from within the eye. Failure of the aqueous balance (e.g., due to blockage in the normal outflow channels) leads to increased pressure within the eye, damage to the optic nerve, and subsequent loss of visual function. The loss of vision is almost always gradual and without concomitant pain. The portions of the eye involved with peripheral or side vision are usually affected first and visual loss is often not noticed by the patient until a large portion of the visual field is destroyed.

There are more than 49,000 people 65 years of age and older, blind from glaucoma, accounting for 11 percent of all blindness in the United States. Despite widespread community and industrial glaucoma screening programs, this disease remains a leading cause of blindness and visual disability.

Blindness from glaucoma usually can be prevented if the disease is detected early and treated promptly. An array of drugs has been developed to control the elevated pressure within the eye. For those fortunate enough to have their condition detected before serious visual loss occurs, the condition often can be stabilized. For those who cannot be helped by medication, surgery is sometimes successful. However, it is impossible to restore vision already lost through glaucoma. Furthermore, existing glaucoma drugs are expensive, inconvenient to use and are often uncomfortable for the patient. These drugs

are also variable in their efficacy and in the incidence of undesirable side effects they produce. New methods for early detection, improved therapeutic and pharmacological techniques, and means of reversing early visual loss are necessary to check this leading cause of blindness and visual disability. Before further progress can be made, however, a better understanding of how increased pressure within the eye leads to loss of vision is vital.

Program Plans for 1976

Although both research and improved patient care have increased the reliability of diagnosis and the effectiveness of therapy for glaucoma, continued investigation is needed in virtually all aspects of glaucoma. In FY 1976, studies will be initiated or expanded in the following areas: (1) the fundamental mechanisms for the formation of aqueous humor, the blockage of which leads to elevated intraocular pressure and possibly glaucoma; (2) the pathways for aqueous humor flow, and the factors responsible for regulation of pressure within the eye; (3) noninvasive methods for studying aqueous humor dynamics, reducing aqueous flow, and enhancing aqueous outlfow, and (4) research designed to predict, with increasing accuracy, the risk of an individual suffering an attack of acute glaucoma.

Accomplishments for 1975

Research into glaucoma has continued to be highly productive both in advancing scientific knowledge and in improving clinical care of patients afflicted with glaucoma.

A system for the noninvasive continuous measurement of pressure within the eye has been developed and is being tested on animals. This system involves the mounting of a miniature sensor in soft contact lens material. The device is placed under the eyelid and transmits via a radio telemetry system to a transcriber console which receives, displays, and records the monitored pressure. Once it is perfected, this device will allow continuous monitoring to detect normal variations in pressure occurring throughout the day and night and to evaluate the effects of various drugs used in the control of glaucoma.

Research involving steroid hormones and their effects on the pressure within the eye has led to the definition of three groups of glaucoma patients referred to as high, moderate and low responders. The categorization of patients into these groups may permit the identification of individuals who are predisposed to elevated intraocular pressure and glaucoma.

Studies concerned with controlling and reducing pressure within the eye have led to the finding that a marijuana derivative may have a beneficial effect. When this drug was injected in rabbits, intraocular pressure decreased and fluid outflow facility and the level of protein in the fluid increased.

A new practical clinical instrument has been developed to measure eye fluid outflow facility by a method referred to as Constant Pressure Tonography. The accuracy with this instrument can lead to a significant improvement in the differential diagnosis of glaucoma. Laboratory testing and validation of the instrument are now underway.

Sensory-Motor Disorders and Rehabilitation

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses.....		$7,459,000		$6,247,000		-$1,212,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting.....	86	4,569,000	88	4,315,000	+ 2	- 254,000
Competing.....	47	1,596,000	9	598,000	-38	- 998,000
Special.....	6	181,000	7	175,000	+ 1	- 6,000
Subtotal.....	139	6,346,000	104	5,088,000	-35	- 1,258,000
Fellowships.....	48	720,000	48	716,000	--	- 4,000
Training Grants.....	27	393,000	12	443,000	-15	+ 50,000
Research & Development Contracts.....	--	--	--	--	--	--
Total.....		$7,459,000		$6,247,000		-$1,212,000

NOTE: Numbers for training grants reflect full-time equivalents.

Introduction

Disorders of the eye and of the visual nervous system that interfere with the normal reception, transmission and processing of visual information by the eye and by the brain are known as sensory disorders of vision. Conditions that involve the ocular muscles and interfere with the normal positioning of the eyes and with the normal movements of the eyes are called oculomotor disorders. As a group, sensory and oculomotor disorders include strabismus (misalignment of the eyes, cross-eye), amblyopia (decreased vision related to developmental problems in the early period of life), errors of refraction, and numerous other conditions which may affect the performance of the eyes in their optical processing of light, the processing by the brain necessary for the maintenance and performance of visual function, or the positioning of the ocular muscles.

There are approximately 31,500 people in this country who are blind from optic nerve atrophy alone. These account for 9.2 percent of all cases of legal blindness, and an estimated 3,000 more individuals become blind from this disorder each year. Not as serious, but definitely more pervasive, are refractive errors. While milder refractive problems are easily corrected with lenses (eyeglasses, contact lenses) advanced and progressive states result in uncorrectable low vision and blindness. Of all causes of visual disability, sensory and motor disorders are among the least understood. Such oculomotor conditions as strabismus, which has serious effects on sensory functions, can be cosmetically corrected in the young child--but often only after extensive visual training or after numerous surgical attempts. Moreover, its treatment

is not generally successful in older children or adults. (Nor is it clear that the available therapies result in improved visual function for many patients). Clearly, a better understanding of the visual sensory and oculomotor systems in health and disease is needed to solve the many clinical problems which exist in this area.

Program Plans for 1976

Because there is need to maintain and build on current knowledge covering the structure and function of the visual sensory and oculomotor systems, and to apply this knowledge to the prevention, diagnosis and treatment--including rehabilitation--of visual disorders, research in the following areas will be emphasized: (1) further studies of strabismus and amblyopia, especially in primates; (2) physiologic, neurochemical, and pharmacologic studies of oculomotor control, particularly in monkeys; (3) research leading to the prevention of degenerative, high myopia and to the changes associated with this condition that may endanger sight; and (4) research on neural mechanisms in the sensory system, and their correlation with clinical findings in sensory and motor disorders of vision, will be directed toward maximization of vision which remains after disease of the visual nerve pathways to the brain.

Accomplishments for 1975

The Institute has supported the development of diagnostic procedures which permit the early identification of amblyopic and strabismic low visual acuity. These involve the application of psychophysical techniques as well as recently developed electroencephalographic techniques.

Researchers have also studied various types of eye movements to determine how they are involved in the maintenance of visual function, as well as how the nervous system and extraocular muscles operate. Such knowledge is integral to treatment and amelioration of cosmetic and functional oculomotor disorders.

Evaluations of various agents as pharmacologic alternatives for the correction of strabismus in monkeys are being conducted. One drug tested has demonstrated prolonged immobilization of the injected muscle without local or systemic side effects. In some cases permanent realignment of the eye was obtained.

Institute supported investigators have successfully mapped the projection of retinal stimulation to some parts of the visual cortex and to other areas of the brain. Anatomical techniques for mapping neural pathways have been developed, and simplified by NEI supported investigators. These very recent developments are helping to identify and define the fashion in which the more than 100 million channels of the human visual nervous system are organized so as to allow for the experience of vision. Then, too, these recent efforts hold great promise towards elucidating the roles of neural structures in disorders such as amblyopia, poor visual acuity, low vision, color blindness and neural blindness.

Intramural Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act, Title IV, Part F

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	84	$1,471,000	76	$1,690,000	-8	+$219,000
Other expenses.....	--	3,429,000	--	3,338,000	--	- 91,000
Total.....	84	$4,900,000	76	$5,028,000	-8	+$128,000

Introduction

The Intramural Laboratory and Clinical Research program of the National Eye Institute is focused on developing new and improved techniques for the prevention, diagnosis and treatment of vision disorders. The Institute's intramural research program is comprised of a Laboratory of Vision Research which conducts studies on the structure and function of the visual system, and a Clinical Branch which applies laboratory knowledge to improved health care and the prevention of visual disorders. The expertise centered in the Clinical Branch and Laboratory of Vision Research serve as an invaluable resource for all Institute programs. In general, the scientific direction of the Institute is greatly dependent upon this highly-regarded corps of professionals, many of whom are internationally known for their research contributions.

Program Plans for 1976

The Laboratory of Vision Research will continue to develop areas of research that will provide better insight into disease processes and the function of visual systems. Animal models to study retinitis pigmentosa will continue to be used to determine the primary event that triggers the process of this retinal dystrophy. Biochemical and immunological studies will be conducted to determine if there are specific protein antigens in the cornea that are responsible for cornea graft rejections. Since Laboratory of Vision Research scientists have uncovered the basic mechanisms that are involved in cataracts associated with diabetes and galactosemia, it is now possible, in animals, to delay the onset of these cataracts with chemical agents. Follow-up experiments for effecting delay or prevention of cataracts based on these developments will be explored.

A prime objective of the Clinical Branch in 1976 is the establishment of a special clinic for diagnosing and treating congenital and developmental defects of the eye. In particular, emphasis will be given to testing a new theory on the treatment of eye problems associated with albinism and aniridia (hereditary failure of the iris to develop). Additional studies will be conducted on a broad array of chemical substances which may be useful in the detection and diagnosis of ocular tumors, in order that eyes need not be removed unnecessarily or conversely, if malignancy is confirmed that lives may be saved. A more thorough analysis of data on the epidemiology of diabetic retinopathy among the Pima Indians, a tribe with the highest prevalence of diabetes of any known ethnic group, will be continued. Such studies may reveal important information on factors associated with both the general disease and its effects on the eye. Other studies being actively pursued include the effect of early treatment of high pressure within the eye and the

evaluation of vitrectomy in attacking the problem of new vessel formation, especially in diabetic retinopathy.

The surgical specimens obtained from vitrectomy are being separated into several components which are examined for the presence of a factor that may be the cause of new vessel formation. Tissue culture techniques are being developed for the study of tissues from the eye of patients with diabetes and simple glaucoma in an effort to discover more about the underlying causes of these diseases. Techniques are being developed for the application of new techniques to the study of retinal degenerations. A controlled clinical trial of urokinase for the treatment of occlusion of the central vein is a major project for the next two years. The investigation of the mechanism of action of drugs used in the treatment of glaucoma is continuing.

Accomplishments for 1975

The Laboratory of Vision Research continued to pursue research aimed at providing better insight into disease processes and the function of the visual system. Animal models to study retinitis pigmentosa were developed to determine the primary event that triggers the process of this retinal dystrophy. Biochemical and immunological studies were conducted to determine if there were specific protein antigens in the cornea that were responsible for cornea graft rejections. Since Laboratory of Vision Research scientists have uncovered the basic mechanisms that are involved in cataracts associated with diabetes and galactosemia, it is now possible, in animals, to delay the onset of these cataracts with chemical agents. Follow-up experiments for effecting delay or prevention of cataracts based on these developments will be explored.

During 1975 the Clinical Branch conducted studies on: (1) patients with ocular melanomas (tumors) to develop improved methods of diagnosis and treatment; (2) retinal function in various forms of retinitis pigmentosa and related diseases in an effort to arrive at more precise diagnostic criteria and prognosis; (3) patients who have undergone immunologic rejection of corneal grafts to determine the relationship of the development of antibodies against the antigens of the donor when the corneas are regrafted; and (4) the problem of new vessel formation and vitreous hemorrhage, which will be attacked by the development of improved instruments using ultrasonic driven cutters to remove strands of vitreous humor. Clinical Branch investigators have also developed an animal model useful for studying the effects of chronic evaluation of intraocular pressure in glaucoma, which will provide a tool for future studies on why and how glaucoma causes visual loss.

Investigation of the relationship of simple glaucoma to the inhibition by glucocorticoids of lymphocyte transformation is being continued. Eventually this study should indicate whether a genetic defect may be the basis for the development of simple glaucoma.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Title IV, Part F

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	58	$1,102,000	56	$1,283,000	-2	+$181,000
Other expenses	--	1,510,000	--	1,329,000	--	- 181,000
Total	58	$2,612,000	56	$2,612,000	-2	--

Introduction

This program provides support for the Office of the Director, NEI, which has responsibility for overall administrative management and scientific direction of Institute programs. The Office of Biometry, Epidemiology and Field Studies, which conducts research and provides statistical and epidemiological support on the incidence and prevalence of visual disorders is also included here. Funds are also provided for salaries and other expenses of the Office of the Associate Director for Extramural and Collaborative Programs. The OD staff of the NEI is the smallest of the research institutes at the NIH.

Program Plans for 1976

Program planning, analysis and evaluation activities will receive particular emphasis by the Institute in 1976. Recommendations of the National Advisory Eye Council for achieving program balance and providing guidance as to future directions of the Institute will be evaluated and implemented where appropriate. The Office of Extramural and Collaborative Programs has developed a more sophisticated and responsive computer-based information system which will produce information relative to grants and contracts on a program basis. In addition to providing overall leadership to the Institute, the Office of the Director is currently engaged in the planning stage of a proposed U.S.-Japan vision research program.

The Office of Biometry and Epidemiology will continue the Framingham Eye Study, the evaluation, consolidation and improvement of national statistics on the incidence and prevalence of eye diseases, and the evaluation of the data collected in the Collaborative Diabetic Retinopathy Study. Additionally, the OBE will coordinate a large-scale clinical trial in vitrectomy, a new surgical technique that holds promise as a treatment for blindness and disability from diabetic retinopathy and other eye diseases.

Continued emphasis will be placed on insuring effective management of limited resources in order to consolidate and build upon the past research accomplishments supported by the Institute.

Accomplishments for 1975

Staff members and outside experts are collaborating with a planning committee of the National Advisory Eye Council to finalize methods of achieving program balance and recommending future directions for NEI supported vision research.

The functions of the Office of Scientific Reports and Program Planning Coordination have been expanded to include all program planning activities for

the Institute. This Office has also begun to document the long-term vision research accomplishments supported by NEI and has provided support services for the planning and evaluation activities of the National Advisory Eye Council.

The Office of Biometry and Epidemiology has been engaged in a wide variety of activities relating to methods of diagnosis, measurement of the extent of eye disease, identification of factors related to disease risk and objective comparisons of alternative treatments. These involved combination of direct research activities by the staff, and assistance or consultation to others in the field of vision research. Examples of major research efforts of this branch are (1) studies to determine the prevalence of visual disorders and the incidence and prevalence of blindness in the United States. Firm data here is critical to management of the national effort in vision research; (2) the Framingham Eye Study which has as its aim the identification of individuals among the Framingham Heart Study population who at the present time have one or more of the four most common causes of adult blindness, that is, senile cataract, senile macular degeneration, chronic simple glaucoma, and diabetic retinopathy. In addition to determining the prevalence of these diseases, which will enhance the national study mentioned above, it is hoped that risk factors that may contribute to these diseases can also be identified; (3) finally, one of the most important activities of the NEI, has been the Collaborative Diabetic Retinopathy Study. This is a cooperative clinical trial to determine whether photocoagulation can delay the onset of blindness in proliferative diabetic retinopathy.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Retinal and Choroidal Diseases
(Public Health Service Act, Title IV, Parts F and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$14,016,000	Indefinite	--	$12,031,000

Purpose: The retina program of the National Eye Institute supports research to obtain a better understanding of how the retina responds to light and converts it into electrical signals that travel to the brain resulting in sight. It also includes research to advance understanding of how the retina is damaged by disease, to develop methods of prevention, early detection, and treatment of retinal disease, and development of animal models of various retinal diseases to facilitate laboratory and clinical research.

Explanation: This program is supported through the awarding of research and training grants to universities and other non-profit institutions, the awarding of fellowships to individuals, research and development contracts, and studies conducted by the Office of Biometry and Epidemiology.

Accomplishments in 1975: During 1975, progress in research against retinal and choroidal diseases has been made in the following areas: (a) refinement of techniques which allow surgeons to simultaneously cut vitreous fibers, remove them from the eye, and replace the vitreous with a balanced salt solution; (b) methods of studying a variety of conditions of retinal toxicity and degeneration in which retinal blood flow is an important factor have been developed; (c) studies to analyze the efficiency of argon laser burns in blood vessel closure or obliteration, and factors relating to the movement of fluid between various retinal and choroidal components have been designed.

Objectives for 1976: Research in the following areas will be stimulated: (1) pigment epithelium research in normal and abnormal retinal function; (2) studies of the organizational structure of the retina and how it processes visual information; (3) studies of retinal pigmentary disorders and retinal storage diseases encompassing a detailed study of retinal biochemistry; (4) the role of retinal and choroidal circulation in diabetic retinopathy and macular degeneration; (5) development of animal models for inflammatory diseases of the choroid and retina; (6) clinical correlations with histologic, biochemical, and physiological abnormalities observed in the retina and choroid.

NATIONAL INSTITUTES OF HEALTH

National Eye Institutes

Program Purpose and Accomplishments

Activity: Corneal Diseases
(Public Health Service Act, Title IV, Parts F and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$6,596,000	Indefinite	--	$5,202,000

Purpose: The NEI corneal disease program is aimed at reducing the impact of this leading cause of visual disability through improved methods of treatment, prevention, and diagnosis.

Explanation: This program is supported through the awarding of research and training grants to universities and other non-profit institutions, the awarding of fellowships to individuals, research and development contracts, and studies conducted by the Office of Biometry and Epidemiology.

Accomplishments in 1975: The transport of sodium, chloride, and other ions across the cornea has been studied in order to clarify how its thin layers of cells (epithelium and endothelium) regulate the amount of water in the cornea. This work has resulted in better understanding of the body's normal mechanisms for keeping the cornea transparent. An antiviral drug (adenine arabinoside) has been found very effective against herpes simplex virus when applied topically. Another development stemming from basic research is a new medium which allows longer storage of corneas before transplantation. Cornea storage time has been prolonged from a few hours to five or six days. The soft contact lens has proven useful in treating many kinds of cornea disease. The use of long-acting antibiotic drugs to prevent secondary infections in trachoma is a significant new chemotherapeutic approach for the treatment of this important public health problem.

Objectives for 1976: Major needs and opportunities in corneal diseases research to be emphasized are: (1) Tissue culture and biochemical analysis of diseased human corneal tissue removed at the time of corneal transplantation including the rejection of corneal grafts; (3) additional controlled clinical trials of new antiviral drugs useful in treating herpes simplex and other important infective diseases of the cornea; and (4) the possible role of viruses in causing tumors of the cornea and conjuctiva.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Cataract
(Public Health Service Act, Title IV, Parts F and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$3,445,000	Indefinite	--	$3,189,000

Purpose: A cataract is a cloudiness or opacity in the lens of the eye, which interferes with the transmission of light to the retina. The NEI cataract program supports research to identify the causes of this disorder and develop methods for its prevention and improved treatment.

Explanation: This program is supported through the awarding of research and training grants to universities and other non-profit institutions, the awarding of fellowships to individuals, research and development contracts, and studies conducted by the Office of Biometry and Epidemiology.

Accomplishments for 1975: The structure of proteins in the lens has been further elucidated. Studies were conducted on solutions separated biochemically from the lens. Research was then conducted to discover whether or not such aggregates can be detected within the intact lens. A method has been devised in which the size of proteins in the intact lens can be measured optically. This discovery now opens the door to a series of investigations of the state of proteins in normal and various types of cataractous lenses. An enzyme having an unusual sensitivity to glucose concentration has been discovered. This finding indicates that an enzyme may be responsible for the development of the types of cataract normally found in children.

Objectives for 1976: Major needs and opportunities in cataract research to be stressed are: (1) the mechanisms which lead to lens opacification, including investigations of the biochemical and biophysical processes operative in the maintenance of normal lens hydration, particularly in primates and human beings, are important and will be studied: (2) the study of protein changes in the lens and the role of protein aggregation in the development of cataracts will receive increased emphasis; and (3) the search for new animal models for studying congenital cataracts and for investigating the degenerative processes associated with aging and cataract production will be encouraged.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Glaucoma
(Public Health Service Act, Title IV, Parts F and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$5,012,000	Indefinite	--	$4,892,000

Purpose: Glaucoma is a group of diseases characterized by loss of visual function associated with damage to the optic nerve and increased pressure within the eye. The NEI glaucoma program supports research on the cause of glaucoma, development of techniques for prevention and early detection of the disease, and improved methods of treatment.

Explanation: This program is supported through the awarding of research and training grants to universities and other non-profit institutions, the awarding of fellowships to individuals, research and development contracts, and studies conducted by the Office of Biometry and Epidemiology.

Accomplishments in 1975: A system for the noninvasive continuous measurement of pressure within the eye has been developed and is being tested on animals; research involving steroid hormones and their effects on the pressure within the eye has led to the definition of three groups of glaucoma patients referred to as high, moderate and low responders. The categorization of patients into these groups may permit the identification of individuals who are predisposed to elevated intraocular pressure and glaucoma; studies concerned with controlling and reducing pressure within the eye have led to the finding that a marijuana deriviative may have a beneficial effect; and a new practical clinical instrument has been developed to measure eye fluid outflow facility by a method referred to as constant pressure tonography.

Objectives for 1976: In FY 1976, studies will be initiated or expanded in the following areas: (1) the fundamental mechanism for the formation of aqueous humor, the blockage of which leads to elevated intraocular pressure and possibly glaucoma; (2) the pathways for aqueous humor flow, and the factors responsible for regulation of pressure within the eye. (3) noninvasive methods for studying aqueous humor dynamics, reducing aqueous flow, and enhancing aqueous outflow, and (4) research designed to predict. with increasing accuracy, the risk of an individual suffering an attack of acute glaucoma.

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NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Sensory and Motor Disorders and Rehabilitation
(Public Health Service Act, Title IV, Parts F and I)

1975 Estimate			1976	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$7,459,000	Indefinite	--	$6,247,000

Purpose: The sensory and motor program of the National Eye Institute supports laboratory and clinical investigations of the optic nerve and the development and function of those activities of the brain and the eye muscles which make vision possible. Support is also provided for the development of rehabilitation techniques and vision substitution devices.

Explanation: This program is supported through the awarding of research and training grants to universities and other non-profit institutions, the awarding of fellowships to individuals, research and development contracts, and studies conducted by the Office of Biometry and Epidemiology.

Accomplishments in 1975: Diagnostic procedures have been developed which permit the early identification of patients with amblyopic and strabismic low visual acuity; researchers have studied the various types of eye movements to determine how they are involved in the maintenance of visual function, as well as how the nervous system and extraocular muscles operate; evaluations of various agents has pharmacologic alternatives for the correction of strabismus in monkeys are being conducted; and Institute supported investigators have also successfully mapped the projection of retinal stimulation to some parts of the visual cortex and to other areas of the brain. Anatomical techniques for mapping neural pathways have been developed and simplified by NEI supported investigators.

Objectives for 1976: (1) Further studies of strabismus and amblyopia, especially in primates; (2) physiologic, neurochemical, and pharmacologic studies of oculomotor control, particularly in monkeys; (3) research leading to the prevention of degenerative high myopia and to the prevention of the changes associated with this condition that may endanger sight; and (4) research on neural mechanisms in the sensory system, and their correlation with clinical findings in sensory and motor disorders of vision will be directed toward maximization of vision which remains after disease of the visual nerve pathways of the brain.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Intramural Laboratory and Clinical Research
(Public Health Service Act, Title IV, Parts F)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
84	$4,900,000	Indefinite	76	$5,028,000

Purpose: The intramural laboratory and clinical research program of the National Eye Institute is focused on developing new and improved techniques for the prevention, diagnosis, and treatment of vision disorders.

Explanation: The Institute's intramural research program is comprised of a Laboratory of Vision Research which conducts studies on the fundamental disease processes of the eye and structure and function of the visual system, and a Clinical Branch which applies laboratory knowledge to improved health care and the prevention of visual disorders.

Accomplishments in 1975: The Laboratory of Vision Research has developed animal models to study retinitis pigmentosa to determine the primary event that triggers the process of this retinal dystrophy; biochemical and immunological studies were conducted to determine if there were specific protein antigens in the cornea that were reponsible for cornea graft rejections. The Clinical Branch conducted studies on: (1) Patients with ocular melanomas (tumors) to develop improved methods of diagnosis and treatment; (2) retinal function in various forms of retinitis pigmentosa and related diseases in an effort to arrive at more precise diagnostic criteria and prognosis; (3) patients who have undergone immunologic rejection of corneal grafts to determine the relationship of the development of antibodies against the antigens of the donor when the corneas are regrafted; and (4) the problem of new vessel formation and vitreous hemorrhage, which will be attacked by the development of improved instruments using ultrasonic driven cutters to remove strands of vitreous humor. Clinical Branch investigators have also developed an animal model useful for studying the effects of chronic elevation of intraocular pressure in glaucoma, which will provide a tool for future studies on why and how glaucoma causes visual loss.

Objectives for 1976: Biochemical and immunological studies will be conducted to determine if there are specific protein antigens in the cornea that are responsible for cornea graft rejections; follow-up experiments for effecting delay or prevention of cataracts will be explored; a special clinic for diagnosing and treating congenital and developmental defects of the eye will be established; studies will be conducted on a broad array of chemical substances which may be useful in the detection and diagnosis of ocular tumors; and the evaluation of vitrectomy in attacking the problem of new vessel formation will pursued.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Research Management and Program Services
(Public Health Service Act, Title IV, Parts F)

1975 Estimate			1976	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
58	$2,612,000	Indefinite	56	$2,612,000

Purpose: This program provides support for the Office of the Director, National Eye Institute, which has responsibility for overall administrative management and scientific direction of Institute programs. Funds are also provided for salaries and other expenses of the Office of the Associate Director for Extramural and Collaborative Programs.

Explanation: This office is reponsible for the management of research grant, fellowship and training grant programs sponsored by the Institute, for the development and implementation of contract supported research programs, and the overall direction of the direct research programs of the Institute.

Accomplishments in 1975: Staff members and outside experts are collaborating with a planning subcommittee of the National Advisory Eye Council to finalize methods of achieving program balance and recommending future directions for NEI supported vision research. The functions of the Office of Scientific Reports and Program Planning Coordination have been expanded to include all program planning activities for the Institute. This Office has also begun to document the long-term vision research accomplishments supported by NEI. The Office of Biometry and Epidemiology has been engaged in the following studies: (1) studies to determine the prevalence of visual disorders and the incidence and prevalence of blindness in the United States. Firm data here is critical to management of the national effort in vision research; (2) the Framingham Eye Study which has as its aim the identification of individuals among the Framingham Heart Study population who at the present time have one or more of the four most common causes of adult blindness.

Objectives for 1976: Program planning, analysis and evaluation activities will receive particular emphasis by the Institute in 1976. The Office of Extramural and Collaborative Programs has developed a more sophisticated and reponsive computer-based information system which will produce information relative to grants and contracts on a program basis. The Office of Biometry and Epidemiology will continue the Framingham Eye Study, the evaluation, consolidation and improvement of national statistics on the incidence and prevalence of eye diseases, and the evaluation of the data collected in the Collaborative Diabetic Retinopathy Study. Additionally, the OBE will coordinate a large-scale clinical trial in vitrectomy, which holds promise as a treatment for diabetic retinopathy.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation.....	$39,201,000	$9,800,000
Total obligations.....	$39,201,000	$9,800,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Retinal and Choroidal Diseases	--	$12,031,000	--	$3,016,000
Corneal Diseases	--	5,202,000	--	1,310,000
Cataract	--	3,189,000	--	773,000
Glaucoma	--	4,892,000	--	1,296,000
Sensory-Motor Disorders and Rehabilitation	--	6,247,000	--	1,495,000
Intramural Laboratory and Clinical Research	76	5,028,000	76	1,257,000
Research Management and Program Services	56	2,612,000	56	653,000
Total, obligations	132	$39,201,000	132	$9,800,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions.....	132	132
Full-time equivalent of all other positions.....	6	6
Average number of all employees.....	127	127
Personnel compensation:		
Permanent positions.....	$ 2,392,000	$ 598,000
Positions other than permanent.....	188,000	47,000
Other personnel compensation.....	80,000	20,000
Subtotal, personnel compensation.....	2,660,000	665,000
Personnel benefits.....	313,000	78,000
Travel and transportation of persons....	90,000	25,000
Transportation of things.....	4,000	1,000
Rent, communications and utilities.....	139,000	35,000
Printing and reproduction.....	60,000	15,000
Other services:		
Project contracts.....	2,322,000	580,000
Payment to NIH Management Fund.....	2,950,000	738,000
Other.....	609,000	149,000
Supplies and materials.....	317,000	79,000
Equipment.....	498,000	125,000
Grants, subsidies and contributions.....	29,239,000	7,310,000
Total, obligations by object.....	$39,201,000	$9,800,000

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the National Eye Institute consistent with the 1976 estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCE

WITNESSES

DR. RUTH L. KIRSCHSTEIN, DIRECTOR
DR. RONALD LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DR. LEO HANS VON EULER, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
DR. ARTHUR E. HEMING, ASSOCIATE DIRECTOR FOR PROGRAM ACTIVITIES, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
GORDON J. KLOVDAHL, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
MRS. EMMA LOUISE AKERS, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES
B. F. GARDNER, JR., CHIEF BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We now have the National Institute of General Medical Sciences.

The presentation will be made by Dr. Ruth L. Kirschstein.

We have your biographical sketch which we will place in the record at this point.

[The biographical sketch follows:]

Name: Ruth L. Kirschstein.
Position: Director, National Institute of General Medical Sciences.
Birthplace and date: Brooklyn, N.Y., October 12, 1926.
Education: A.B., Long Island University, 1947; M.D., Tulane University School of Medicine, 1951.

Experience

Director, National Institute of General Medical Sciences, September 1974-present;
Deputy Associate Commissioner for Science, FDA, 1973–1974;
Acting Deputy Director, Bureau of Biologics, FDA, 1972–1973;
Assistant Director, Division of Biologics Standards, NIH, 1971–1972;
Chief, Laboratory of Pathology, DBS, NIH, 1965–1972;
Acting Chief, Laboratory of Pathology, DBS, NIH, 1964–1965;
Assistant Chief, Laboratory of Viral Immunology, and Chief, Section of Pathology, DBS, NIH, 1962–1964;
Chief, Section of Pathology, Laboratory of Viral Immunology, DBS, NIH, 1960–1962;
Medical Officer, Pathologist, Laboratory of Viral Products, DBS, NIH, 1957–1960;
Medical Officer, Resident in Pathology, Clinical Pathology, Clinical Center, NIH, 1956–1957;
Trainee of National Heart Institute and Instructor in Pathology, Tulane University School of Medicine, 1954–1955;
Resident, Pathology, Providence Hospital, Detroit, Mich., 1952–1954;
Assistant Resident, Pathology, Veterans Administration Hospital, Chamblee, Ga., 1952;
Internship, Medicine and Surgery, Kings County Hospital, Brooklyn, N.Y., 1951–1952.

Association memberships

American Association of Immunologists;
American Association of Pathologists and Bacteriologists;
American Society of Microbiology;
Washington Pathology Society.

Special awards and citations

Invited member of World Health Organization Expert Group on International Requirements for Biological Substances, Geneva, Switzerland, March 1965 and 1971;
Invited consultant to World Health Organization concerning problems related to the use of Poliovirus Vaccine, Live, Oral, Geneva, Switzerland, March 1967;
Member of Ad Hoc Task Group for Interferon Research, NIAID, 1969 to present;
DHEW Superior Service Award, 1971;
Member, Board of Consultants, Journal of Medical Primatology, 1971;
Member, Program Committee, American Association of Immunologists;
Member, Primate Research Center Advisory Committee, Division of Research Resources, NIH.

Selected publications

Kirschstein, R. L., Baron, S., Borman, G., Murray, R., Perkins, F. T., and Hottle, G.: Neurovirulence of attenuated Type I poliovirus vaccine strains after intramuscular inoculation of rhesus monkeys. Virology 11:300–302, May 1960.
Kirschstein, R. L. and Gerber, P.: Ependymomas produced after intracerebral inoculation of SV40 into newborn hamsters. Nature 195:299–300, July 1962.
Kirschstein, R. L., Rabson, A. S., and Peters, E. A.: Oncogenic activity of adenovirus 12 in thymectomized BALB/c and C3H/HeN mice. Proc. Soc. Exp. Biol. Med. 117:198–200, 1964.
Kirschstein, R. L., Rabson, A. S., and O'Conor, G. T.: Ependymomas produced in Syrian hamsters by adenovirus 7, strain E46 ("hybrid" of adenovirus 7 and SV40). Proc. Soc. Exp. Biol. Med. 120:484–487, 1965.
Kirschstein, R. L., Rabson, A. S., Paul, F. J., and Peters, E. A.: Double infection of newborn Syrian hamsters with simian virus 40 and human adenovirus 12. Cancer Res. 26:1361–1364, July 1966.
Kirchstein, R. L.: Value of neurovirulence tests for attenuated vaccine assessment International Symposium on Neurovirulence, Munich 1965. Symp. Series Immunobiol. Standard 2:267–268 (Karger, Basel/New York 1966).
Kirschstein, R. L. and Clark, G.: Reproducibility of neurovirulence tests. International Symposium on Neurovirulence, Munich 1965. Symp. Series Immunobiol. Standard 2:141–150 (Karger, Basel/New York 1966).
Kirschstein, R. L., Smith, K. O., and Peters, E. A.: Inhibition of adenovirus 12 oncogenicity by adeno-associated virus. Proc. Soc. Exp. Biol. Med. 128:670–673, 1968.
Kirschstein, R.L. and Palmer, A. E.: A primate program developed for the testing of biological products. Proceedings of the Second Conference on Experimental Medicine and Surgery in Primates, Medical Primatology 886–894, Ed.—E. I. Goldsmith and J. Moor-Jankowski, Basel S. Karger, 1970.
Kirschstein, R. L., Rabson, A. S., and Rusten, G.: Infiltrating duct carcinoma of the mammary gland of a rhesus monkey after administration of an oral contraceptive. J. Nat. Cancer Inst. 48:551–556, 1972.
Kirschstein, R. L.: Cyclamates. Human Pathology, 5:498, July 1974.

Mr. FLOOD. Do you have some people with you that you would like us to meet?

Dr. KIRSCHSTEIN. Yes, sir.

To my left is Mr. Gordon Klovdahl, the Executive Officer and to his left Dr. Leo von Euler, the Deputy Director of the Institute. Behind Mr. Klovdahl is Mrs. Emma Louise Akers, the Financial Management Officer, and behind Dr. von Euler is Dr. Arthur Heming, the Associate Director for Program Activities.

Mr. FLOOD. All right.

You have a statement here. How do you want to handle this?

Dr. KIRSCHSTEIN. I would like to read it if I may.

Mr. FLOOD. Suppose you do.

Dr. KIRSCHSTEIN. Mr. Chairman and members of the committee, this is the first time that I appear before you, and I feel that it is an honor to do so. My colleagues and I, indeed, deem it a privilege to be here to describe for you the programs of the National Institute of General Medical Sciences, our accomplishments in the past, and our hopes for the future. As the very name of the Institute implies, our programs must be very broad to encompass support of scientific endeavors in biomedical fields which are basic to understanding of human disease, and in clinical research which is more directly applicable to patients and to the maintenance of health. One of our programs is concerned with the development of knowledge in genetics and the inheritance of disease states or other abnormalities which may increase susceptibility to disease.

GENETICS PROGRAM

For example, a basic biochemical defect which results in extremely high cholesterol levels in the blood and the development of coronary artery disease at a young age has been studied by scientists supported by us. These investigators have shown that the primary genetic abnormality in this condition, familial hypercholesterolemia, is a defect, on the cell surface. Normal cells have a material on their surface that binds circulating serum lipoproteins (complex molecules containing both protein and fats, including cholesterol). The surface material causes the cholesterol component of lipoproteins to split off, enter the cell, and suppress the production of an enzyme which in turn suppresses cholesterol within the cell. The cells of persons with this hereditary condition lack this surface material, and therefore cholesterol production is greatly increased, with resultant increased risk for coronary artery disease. It seems likely that, based on this work, tests can be developed which will indicate this genetic predisposition of individuals and their family members toward coronary artery disease and thus allow preventive measures to be taken. Very recently, these investigators have found that certain chemicals, related to cholesterol, can enter the cells without the aid of the binding factor. These chemicals also inhibit the production of cholesterol by the cells. Thus, there exists the possibility of therapy for this condition and prevention of coronary artery disease and heart attacks. The impact of such diagnostic tools and of therapeutic or, rather, preventive measures would be considerable.

It goes without saying, of course, that, until all of the details of the work are confirmed and the proper reliable tests developed, the final prevention or modification of such a disease is but a hope; a hope, however, based on evidence developed by basic research.

Last year, at this hearing, we presented information concerning the fact that susceptibility to lung cancer seemingly is inherited and that certain people produce an enzyme which converts materials in tobacco smoke to cancer-inducing substances. It seemed possible that a simple test could predict which persons were particularly susceptible. I must tell you that, currently, while the general thesis remains correct, fur-

ther studies by the Institute's grantees as well as others supported by the National Cancer Institute, have indicated that the ability to predict which individuals are at risk is not quite as straightforward as seemed likely 1 year ago. Indeed, new, more reproducible tests are needed and these are currently under development. Nevertheless, it does seem assured that this discovery will eventually have broad implications in the prediction of susceptibility to lung cancer. Of utmost importance is the fact that the research and investigations into this entire matter continued after the first discovery was made, so that the true elucidation of the phenomenon occurred in a timely way and that no screening program was undertaken based only on preliminary data. This story is, of course, the general rule, rather than the exception, and emphasizes why continued support in areas of basic science such as genetics is so essential.

CELLULAR AND MOLECULAR BASIS OF DISEASE PROGRAM

Another major program area of the Institute is focused on the cellular and molecular basis of disease. In the newly emerging science of molecular pathology, investigators analyze the normal structure and function of the cell and its molecular machinery, and relate specific abnormalities to human disease. This will serve as the foundation for better diagnosis and more rational treatment of the full spectrum of human disease. The NIGMS, encouraged by the Congress and this committee, is providing support for molecular pathology centers. The first such center was established in June 1974 at the Yale University School of Medicine under the direction of Dr. George Palade, the Nobel Laureate in Physiology or Medicine for 1974.

Many investigations relate to enzymes, a term I have already mentioned. Let me take a minute to explain what enzymes do generally, for they are, in some respects, the most characteristic elements of life. They are catalysts that allow chemical reactions that would otherwise proceed extremely slowly to proceed much more rapidly at body temperature. Thus, if it were not for trypsin, an enzyme produced by the pancreas and secreted into the small intestine to help digest the proteins in our food, it might take several years to digest just one meal. Since the cell itself is rich in proteins, the biochemists have asked, "Why don't these enzymes digest the very cells that produce them?" The explanation for this was made much clearer in 1955 by two NIGMS grantees, who found that the pancreas produces an inactive precursor which is only activated when it enters the intestine. Trypsin-like enzymes also play an essential role in the clotting process of blood. To regulate and control the activity of these powerful agents, living systems contain complex fail-safe mechanisms that prevent overreaction, or misdirection. Thus, when a blood clot forms, counteracting enzymes and inhibitors limit the extent of the clot to the immediate area of the wound, allowing the normal circulation of blood to continue. Recently it has been shown that in some inherited—and perhaps, also acquired—illnesses, the blood is deficient in circulating trypsin inhibitors and that this deficiency is associated with advanced liver disease and pulmonary emphysema. Furthermore, the importance of the trypsin family of enzymes extends beyond digestion and blood clotting to include a role in

the mediation of pain sensation, immune reactions, and the spread of cancer cells. Basic studies of these enzymes which are currently being supported by NIGMS will have far-reaching effects on our understanding of many medical problems.

PHARMACOLOGY-TOXICOLOGY PROGRAM

Of equal importance to the understanding of abnormalities of cells to disease, is an understanding of the effects of drugs both at a cellular and tissue level. It is only by such knowledge that rational drug therapy for disease can be planned. The pharmacology-toxicology program supports research in the areas of drug metabolism, toxicity of drugs, and also, of most importance, clinical pharmacology programs which are responsible for studying the action of drugs in the patient. Information derived from this program enables the medical profession to use drugs more wisely and gives physicians a better understanding of the interaction of drugs in their patients. Under contract to NIGMS, Dr. Hershel Jick and his colleagues at Boston University search for and elucidate adverse drug reactions and serious side effects. In addition to keeping the practicing physician abreast of developments by numerous reports in medical journals such as the Journal of the American Medical Association and the New England Journal of Medicine, this group is in close contact with the FDA as well as NIH so that prompt attetnion can be given to any unexpected findings which require immediate action by these agencies.

Rational drug therapy should be based on the ability to deliver the correct amount of drug to the site of its action for the desired period of time. The level of the correct amount is very critical since too little drug will not give the needed effect and too much drug may lead to undesired side effects and even serious toxicity. Recently, an NIGMS grantee has found markedly increased concentrations of the drug Valium (a widely prescribed tranquilizer) in the blood of elderly patients compared to the concentration in younger patients after administration of the same dose. Apparently the drug is eliminated from the body four times as slowly and is stored in greater quantities for much longer periods of time in elderly patients than in young ones. Thus, prolonged sedative action and delayed toxic effects will occur in older patients given this tranquilizer at the usually prescribed drug levels. It is clear that the dosage schedule for elderly patients needs to be modified in order to use this most valuable drug wisely. Investigations are currently being undertaken to see if similar situations occur with other drugs.

A grantee of the pharmacology-toxicology program of NIGMS currently is investigating the toxicity of oxygen in the newborn. While oxygen is essential to life, this scientist has shown that hyaline membrane disease, which is usually fatal to premature infants, may develop because of the inability of the fetal lung to metabolize oxygen. Premature infants seem to lack a specific enzyme, called superoxide dismutase, which reduces the toxicity of metabolic byproducts of oxygen in the lungs. The lack of this enzyme, which develops very late in gestation, seems to cause oxygen toxicity and lung damage in prematurely born infants. These preliminary findings, we hope, will

lead to an understanding of the cause of oxygen toxicity and, perhaps, of hyaline membrane disease. From these studies one would hope that a specific therapy or preventative may develop.

CLINICAL AND PHYSIOLOGICAL SCIENCES PROGRAM

As can be seen in the above examples, the NIGMS supports not only basic biomedical research but also clinical research as well. In the clinical area, our efforts are largely concentrated on support for studies in anesthesiology and in trauma and burn injuries. Last year, you were told of the unique success of one of the NIGMS grantees at the Trauma Center in Dallas, Tex., in saving the life of a child with burns that covered 92 percent of the body.

Recently, the Burn Research Center at the Massachusetts General Hospital in Boston has defined the steps that are needed in order to treat successfully persons with burns involving 80 percent or more of the total body surface. The first is the early transplantation of skin grafts from a close relative of the patient. The grafts survive quite well if, at the critical period after grafting, the patient receives drugs called immunosuppressants, which inhibit rejection of the grafts. However, these drugs often lower the body's defenses against infection by bacteria. Thus the second essential is to keep those patients infection-free by placing them in a bacteria-free environment—a "sterile island"—in which even the air they breathe is sterilized. Third, because of a great loss of fluid from the burned surfaces and the body's increased use of energy, enormous intakes of fluids and calories are required. Such calories must be given by hyperalimentation—the use of high caloric, high protein, liquid foods given primarily by stomach tube. Finally, after the temporary grafts have been in place for a few weeks, grafting is started using the patient's own skin. This allows time for the patient to grow new skin as the process heals. The immunosuppressive drugs are discontinued, the patient then can leave the "sterile island," and other procedures can be performed as needed. At present, although this stepwise procedure takes 6 to 7 months, the mortality rate after such severe burn injury has been reduced from almost 100 percent to about 60 percent, a gratifying result which it is hoped will be improved by further research. It is also the aim of such studies to shorten the recovery period considerably.

BIOMEDICAL ENGINEERING PROGRAM

Another NIGMS program which is related to clinical studies is in biomedical engineering. This program is designed to support the effective application of the principles of engineering science to fundamental and applied biomedical research, particularly, to the provision of new, more rapid techniques of diagnosis of disease. For example, diagnostic radiology is dependent on the availability of highly trained radiologists. Since there are not enough such specialists available, patients in remote areas, far from medical centers, often have to wait for long periods of time before X-ray diagnoses can be rendered. Bioengineers at the Massachusetts Institute of Technology, under a grant from our Institute, have developed a prototype device which is controlled by a computer and enables transmission and reproduction of

high quality facsimiles of X-ray films which are virtually indistinguishable from the originals. It uses a laser scanner to convert the light transmitted through radiological films into highly precise electronic signals, which can be transmitted by telephone lines to a central hospital facility where they are reconverted into accurate copies of the original films in a matter of minutes. These films can then be read and interpreted by skilled radiologists who can transmit reports back to the local hospital in a very short period of time. Thus, expert diagnostic capability could be available even to areas in which there is a scarcity of radiologists. This device is currently only in the prototype form and it is expected that it can be manufactured at a modest cost. Encouraged by this committee, the NIGMS is currently planning support for several biomedical engineering research centers.

Mr. Chairman, in order to support programs such as those described above, the budget request for the National Institute of General Medical Sciences for 1976 is $161,630,000. I shall be pleased to try to answer any questions and supply any additional information desired for the record.

NONCOMPETING GRANTS

Mr. FLOOD. Doctor, let's start this session with an explanation of the impact on your program of the proposed budget reduction. You have a reduction of $25,660,000. If we were to approve this budget would you be able to meet all of your noncompeting grant commitments?

Dr. KIRSCHSTEIN. Mr. Chairman, for the commitments we currently have in the research grant area, we will need an additional $3,400,000 in 1976. We could honor these commitments by reducing the moneys to be available for new research grants to $2,900,000. This would support very few new grants in the coming year.

Mr. FLOOD. How much more money would you need to fund all of your noncompeting grants?

Dr. KIRSCHSTEIN. To pay new and competing research grants at the same level in the next year as this year we would need $28 million. This would fund approximately 608 new grants.

TRAINING

Mr. FLOOD. On page 15 of your justifications you state that your Institute has principal responsibility for supporting, through predoctoral training programs, young molecular research scientists. We had the impression from all the witnesses who preceded you that NIH has been deemphasizing the predoctoral training.

What is the situation with regard to predoctoral training grants in your Institute?

Dr. KIRSCHSTEIN. Mr. Chairman, of the predoctoral training that NIH does, our Institute has in the past supported approximately two-thirds of that effort. We, in addition, support, as this indicates, a special program for medical scientists to obtain a combined medical and Ph. D. degree.

Mr. FLOOD. Now, on page 18 of your justifications you show the same dollar level for training grants in 1975 and in 1976. However, the number of grants declines by 120 in 1976.

Now, I don't understand how the dollar level stays the same while the number of projects decline. How do you explain that to us?

Dr. KIRSCHSTEIN. Mr. Chairman, the listing here for training grants refers to the old training grant program of the Institute which is in its phaseout period. These were the training grants that were funded over the years prior to the inception of the new National Research Service Act. The grants are gradually phasing out and the costs will be gradually going down. They are approximately the same at the present time because the same numbers of people are being trained.

Mr. FLOOD. Well, under what legislative authority do you award the 289 training grants in fiscal 1976?

Dr. KIRSCHSTEIN. That is based on the old training grants commitments which were to be permitted to be continued and phased out in an orderly fashion, sir.

Mr. FLOOD. What about the law, what legislative authority do you have? What law and what legislative authority do you have?

Dr. KIRSCHSTEIN. Mr. Chairman, this is under section 104(b) of the Biomedical and Behavioral Research Training Act which indicates that the amendments shall not apply with respect to commitments for research training made before enactment of that act. We will use this while we have commitments on that authority.

Mr. FLOOD. How much of your training commitments in fiscal 1975 were awarded under the authorities of the Biomedical and Behavioral Research Training Act?

Dr. KIRSCHSTEIN. These are listed under the fellowships. Approximately $12 million will be funded under the new National Research Service Act.

Mr. FLOOD. On June 30, 1975, the Biomedical and Behavioral Research Training Act will expire. If an extension of this act is delayed beyond June 30, then what portion of your training program would you have to provide under a continuing resolution?

Dr. KIRSCHSTEIN. We would hope that we will have approximately 1,100 individual fellows in training through the year. We would have to support new awards on a continuing basis until the new legislation could be approved.

Mr. FLOOD. Does that reduction of 514 fellowships in fiscal 1976 reflect the shift in emphasis from predoctoral to postdoctoral training support?

Dr. KIRSCHSTEIN. Partially.

In addition, many of the fellowship awards are for 1 year's training.

Mr. FLOOD. How many individuals would you provide training support for under this budget?

Dr. KIRSCHSTEIN. Eleven hundred fellowships.

Mr. FLOOD. How does that compare with the number of indviduals that you supported in 1975?

Dr. KIRSCHSTEIN. The 1,100 fellowships are for new awards, Mr. Chairman. We are currently supporting approximately 5,000 individuals under training.

Mr. FLOOD. In 1976, how many will you be able to take on?

Dr. KIRSCHSTEIN. Under the funds provided for fellowships in 1976 under the National Research Service Act, we will be able to fund only 30 new grants. However, in the training grants we will have approximately the same assuming we can support predoctoral training.

Dr. LAMONT-HAVERS. Mr. Chairman, as a clarification, as of now we would not intend to make any new predoctoral awards in 1976.

AUTOMATED CLINICAL LABORATORIES AND BIOMEDICAL ENGINEERING

Mr. FLOOD. I wouldn't think so.

Last year we were told that the Stanford Research Institute was about to complete its work on an ultrasonic camera system which would give clear images of the internal organs. What is the present status of that instrument?

Dr. KIRSCHSTEIN. The instrument has been further developed and has been used by this group and by others for imaging techniques, particularly to visualize the fetus during pregnancy. The efforts that are being expended now are primarily aimed at determining whether the ultrasound device will in the long run be without adverse effects on the internal organs and particularly on the fetus.

There is an attempt to determine whether this instrumentation should be very widely used.

Mr. FLOOD. How much would it cost a community hospital to buy and install one of these systems?

Dr. KIRSCHSTEIN. To install this ultrasound instrumentation in a general hospital would cost about $50,000.

COOPERATION WITH C.D.C.

Mr. FLOOD. Now, in your justification, you state that one of your program objectives "is to develop more rational automated laboratory procedures and techniques for use in health care delivery."

Just last week we had Dr. Sencer, the Director of the Center for Disease Control. He told us that of the 1,100 laboratories he inspected, only 882 could meet the standards. How does your Institute work with Dr. Sencer's organization in improving the quality of work done in our Nation's laboratories?

Dr. KIRSCHSTEIN. Dr. Sencer's responsibility is to see, as you said, that the laboratories meet the standards. We, through our support of research efforts, attempt to provide means for these laboratories to provide more rapid diagnostic tests and more automated tests. We keep close contact with Dr. Sencer's groups. We have had meetings with them on many occasions and the information that is developed from our programs is transmitted to them. For example, in the next month we will be having a large meeting concerning laboratory diagnosis and the use of automated equipment in which the state of the art will be redefined and we will bring up to date where we are and Dr. Sencer's people are participating.

NEW LABORATORY TECHNIQUES

Mr. FLOOD. Can you give us some examples of any new laboratory procedures and techniques that have been developed by your Institute in the last 2 or 3 years which are being routinely used in health care.

Dr. KIRSCHSTEIN. Yes.

Mr. FLOOD. If you can, I would like you to tell us how each of these techniques now has improved both the quality of medical care and contributed to the containment of medical care costs.

Dr. KIRSCHSTEIN. Mr. Chairman, under support from NIGMS, an instrument you have heard of many times before, the GeMSAEC instrument, a fast clinical analyzer, was developed. This instrument is currently being used in 350 or 400 hospital laboratories throughout the United States. It has enabled the performance of diagnostic tests using smaller amounts of blood compared to the amounts in the same procedures needed prior to the use of GeMSAEC instrument and has enabled the laboratory to increase its accuracy and speed.

In addition, in about 100 laboratories, there is currently being used a testing procedure for the growth of bacteria causing infection in patients which uses a method developed by a NIGMS grantee. This is the use of radioactive materials in a media selectively used. In determining the particular radioactive material put in the media identification of the bacteria can be performed very rapidly and increase the speed with which the diagnosis on a patient can be made.

Mr. FLOOD. How does that improve the quality of the medical care and contain the cost?

Dr. KIRSCHSTEIN. The cost of the medical care will be lowered because identification of the cause of disease will be markedly hastened and treatment can be started more rapidly and hopefully the number of hospital days can be decreased.

The quality of the medical care would be equally increased again because the patient can be treated more rapidly and in addition I think increased accuracy can occur.

TRAUMA AND BURN RESEARCH

Mr. FLOOD. Last year we were told you planned to have 15 trauma centers established by the end of fiscal year 1975. Did you reach that goal?

Dr. KIRSCHSTEIN. We have nine trauma centers and one burn research center. Now, because many of our trauma centers work not only just on the problems of trauma but on burn injury as well, we wish to consider these centers as trauma and burn research centers. I guess you would say we have 10 if you include the burn research center in Boston. In addition we have applications currently pending for three or four more of these.

We would hope to fund several before the end of the fiscal year.

Mr. FLOOD. But you had planned 15.

Dr. KIRSCHSTEIN. Yes, sir, and that is still our goal. However, some of these are more complex and time consuming than we anticipated.

Mr. FLOOD. What kind of work do you do at these centers?

Dr. KIRSCHSTEIN. These centers engage in research both at the basic and clinical level in an attempt to elucidate the mechanisms by which trauma and burn adversely affect the physiological processes of the body and in an attempt to improve clinical care.

Mr. FLOOD. You say trauma and burn.

Dr. KIRSCHSTEIN. Yes, sir.

We consider burn injury to be a form of trauma.

The centers are an integrated effort between basic and clinical research to elucidate physiologic and cellular levels of injury and move from those findings to improved treatment and care through the use of fluids, et cetera.

Mr. FLOOD. Last year we asked you about these trauma centers, how they were related to the emergency medical system programs which is being administered by the Health Services Administration. Now you told us at that time that they did not work very closely together. Has that situation changed since last year?

Dr. KIRSCHSTEIN. Yes, sir, it has. Currently the burn research center in Boston is working very closely with the Massachusetts State Emergency Medical Service program. In addition our trauma research center in Seattle, Wash., is working closely with that State's emergency medical services program. We have a trauma research center in San Francisco which works with the city emergency medical service program. We have an application or a prospect of an application for a large trauma and burn center in San Diego through the University of California.

There is an emergency medical services program there as well.

Mr. FLOOD. Then you say these are now working closely together.

Dr. KIRSCHSTEIN. Yes, sir. In addition, the Department has an Inter-Departmental Emergency Services Committee. NIH has a representative on that committee. NIH has then formed within its own organization such a committee and we have membership on it.

Mr. FLOOD. We know a good deal about the cancer centers and how they operate as a regional center. Do you have anything in mind for these trauma centers that they do the same sort of thing, act as a regional center?

Dr. KIRSCHSTEIN. We have not specifically had that in mind because these are research centers, Mr. Chairman. They are not purely centers for the care of patients. That is within the emergency medical services' responsibility. We hope our programs in these centers will be an integrated effort of basic and clinical research which can then be translated into care.

GENETICS RESEARCH

Mr. FLOOD. In your opening statement you said that in your genetics program you are working on a test which will indicate genetic predisposition on families toward coronary heart disease. When will the results of that test be available to the general public?

Dr. KIRSCHSTEIN. I do not think we can predict that with certainty. This was a finding which came out of a basic genetics study, which was not designed to work on this problem. I think this is a clear example of why support for basic research is very important.

When the investigator found this, he changed his emphasis and began to work rather directly on this area. It is a relatively new finding.

The investigator has communicated this to the scientific community. The people in the National Heart and Lung Institute are aware of this finding.

A good deal more work needs to be done. We would hope this can be translated as rapidly as possible.

Mr. FLOOD. Last year you told us you were planning to set up a conference of experts and establish guidelines on the genetic counseling. Did you do that?

Dr. KIRSCHSTEIN. Yes, sir.

The conference was an attempt to determine the guidelines needed to evaluate genetic screening and counseling and was held at the end of February and the first day of March. The report is currently being prepared. The conference encompassed social sciences and medical sciences.

Mr. FLOOD. Will you send a copy of that report to the committee?

Dr. KIRSCHSTEIN. Yes, sir. It will be published in the American Journal of Public Health and American Journal of Medical Genetics.

DISSEMINATION OF INFORMATION

Mr. FLOOD. In your statement you talked about the increased concentration of the drug Valium in elderly patients compared to the concentration in younger patients after the administration of the same dosage. That seems to be pretty startling information, especially after we read all the newspaper stories and hear all the stories about the patients in nursing homes who are oversedated, currently especially. How can we communicate this information to the practicing physicians?

Dr. KIRSCHSTEIN. The information has been published in scientific journals. I believe we have a responsibility to communicate it and we are attempting to do so. I think the best way is through journals of AMA and by verbal communication. We encourage the investigators to present this information at medical society meetings.

GENERAL EXPENSES

Mr. FLOOD. On page 7 of your justifications you show a 70-percent increase in what you call, to quote the phrase, "Other services." Now in light of the reduction you told us about in your research grants and contracts, how do you explain that pretty startling increase?

I hope you are not going to tell me that is due entirely to inflation.

Dr. KIRSCHSTEIN. No, sir.

This is due to the increased costs of the general expenses.

Mr. FLOOD. Seventy percent for other services?

Dr. KIRSCHSTEIN. Yes, sir.

Mr. FLOOD. What do you mean by other services?

Dr. KIRSCHSTEIN. The general expenses and program evaluation funds.

Mr. FLOOD. That is quite an umbrella; is it not? Can you tell us a little more about that?

That is pretty general.

Your answer was as general as the heading.

Dr. KIRSCHSTEIN. This is for varying costs that are encumbered through the entire NIH, part of which, for example, will be for the funding of a program that Dr. Lamont-Havers has mentioned, I believe, in his discussions, the need for the anesthesiology service in the clinical center.

Mr. FLOOD. You see why this would stand out like a sore thumb. You reduce your research grants and your contracts markedly and yet right through the ceiling goes a 70-percent increase in this one area of "Other services." That seems to be a nice rug to hide things under in the corner. "Other services," that is a catchall; is'nt it?

Dr. LAMONT-HAVERS. Mr. Chairman, I think we should provide for the record a breakdown of the increase.

Mr. FLOOD. I think you should. That is the understatement of the morning.

[The information follows:]

The object class "Other services" includes such items as data processing, repairs and maintenance of office equipment, storage of household effects, and tuition. It also includes contracts, payment to NIH management fund, and the Institute's share of program evaluation and general expenses. The increase of $701,000 in the "other" line items represents estimated increased costs of data processing and other operating expenses of $88,000 and $613,000 for the Institute's share of the cost of the anesthesiology research and service contract in the Clinical Center.

Mr. FLOOD. Mr. Natcher.

RELATIONSHIP BETWEEN EARCREASES AND CORONARY DISEASES

Mr. NATCHER. Several weeks ago I read an article in one of the magazines which said ear lobes are suspected as furnishing a clue to the absence or presence of heart disease when coupled with other physical symptoms. According to this article the study was made by Dr. Jack Sternleib at Mayo Clinic on 144 patients. He stated there seemed to be a relationship between the presence of the ear creases and diagnostic evidence of the presence or absence of coronary artery disease.

One or two of the Members in the House that I know personally who have suffered severe heart attacks and who are still with us do not have these creases. Since reading this article I have been looking at ears. Several of the Members in the Senate and the House that I know who have heart trouble and who know they have heart trouble have a clear distinct crease, just like you drew a line through both of their earlobes. Are you acquainted with the study? I think I should have stated that this was based only on 144 patients. Are you acquainted with this?

Dr. KIRSCHSTEIN. I saw the same thing you saw in the newspapers, sir. I am not acquainted with it beyond that.

Mr. NATCHER. Of course I know nothing about the validity of this study. As I have stated to you, it is rather unusual, Doctor, that the ones I know who know they have heart trouble, heart disease, they certainly have that crease in both earlobes. I presume judging from the article it is a matter of circulation probably that brings this crease about.

Dr. KIRSCHSTEIN. That is very possible.

Mr. NATCHER. But you are not acquainted with it?

Dr. KIRSCHSTEIN. Not beyond what I saw in the newspaper.

Mr. FLOOD. Can we get something on that?

Dr. KIRSCHSTEIN. We will see what we can learn.

[The information follows:]

The presence of creases in the earlobes is know as McCarthy's sign. It can be unilateral or bilateral and it was described several years ago. It is hereditary and is related to the final embryonic development of the ear. Recent studies have shown that its presence appears to correlate with susceptibility to coronary artery disease. At the present time there is no known cause and effect relationship.

Mr. FLOOD. Mr. Michel.

PRINTING AND REPRODUCTION COSTS

Mr. MICHEL. I note in your justifications an increase for "Printing and Reproduction" of four times over last years estimate—more than $134,000 increase. Certainly the dissemination of information is an important function of the Institute if we are to utilize our research knowledge. However, why such a large increase in a single year? Is there some spectacular new discovery you are trying to advertise?

Dr. KIRSCHSTEIN. The increase of $134,000 for printing and reproduction services in 1976 reflects a more realistic amount than projected in 1975. The increase is due primarily to duplication of research grant and fellowship applications, the number of which has been far greater than anticipated. We are also increasing our efforts in dissemination of information. At present we are reviewing a monograph for the public on the Mutant Cell Bank. Another monograph is in preparation and several others are in the planning stage.

RELATIONSHIP WITH THE DENTAL INSTITUTE

Mr. MICHEL. Regarding the control of pain, the Dental Institute also has a strong interest in this area, including the use of acupuncture. How do your programs relate between the two Institutes and what kind of specific projects have been pursued in this area?

Dr. KIRSCHSTEIN. Pain research is emphasized in both the National Institute of Dental Research and the National Institute of General Medical Sciences. Because of its multicategorical nature, the National Institute of General Medical Sciences is interested in all aspects of pain whereas the National Institute of Dental Research is concerned with oral pain. An example is the anesthesia research center at Seattle, where scientists supported by both Institutes are working side by side. These investigators have applied a method called "sensory decision theory" to approach the study of the effects of various analgesics on pain sensation more objectively. From this method, it should be possible to distinguish between the so-called "physiological" and "psychological" effects of analgesics. Staff of the two Institutes have participated in workshops and jointly supported the International Symposium on Pain held in Seattle, Wash. in May 1973. Also collaborative research occurs among the grantees of the two Institutes is an attempt to relate the various components of the pain syndrome.

BIOMEDICAL ENGINEERING CENTERS

Mr. MICHEL. How many Biomedical Engineering Centers are there now and where are they located?

Dr. KIRSCHSTEIN. There are four Biomedical Engineering Research Centers located at: Case Western Reserve University, Cleveland, Ohio;

University of Washington, Seattle, Wash.; Stanford University, Stanford, Calif.; and at the University of Florida, Gainesville, Fla.

Mr. MICHEL. You indicate you expect to support one or two additional centers in 1976. Do you have any specific locations in mind and where would they be?

Dr. KIRSCHSTEIN. Probably one at Massachusetts Institute of Technology, Cambridge, Mass., depending on the results of merit review.

COORDINATION WITH OTHER INSTITUTES

Mr. MICHEL. Your Institute, of course, has a considerable amount of overlap with other Institutes. With projects like the cholesterol study and the possibility of preventing coronary artery disease and heart attacks and the study of the susceptibility of certain people to lung cancer, how do you go about coordinating with heart and lung and with cancer, respectively?

Dr. KIRSCHSTEIN. These two projects are perfect examples of results from basic research. As promising leads developed which were more disease oriented support from the other Institutes becomes more appropriate. Thus there is complementation but very little, if any, duplication.

Mr. MICHEL. How do you decide whether or not this is an area which is funded by you or is more appropriate in the particular institutes?

Dr. KIRSCHSTEIN. Research grants applications are referred to the several institutes by the Assignment Office of the Division of Research Grants according to published guidelines.

Mr. MICHEL. Since many of your research projects cover a broad base which do overlap with areas under study in specific institutes, what system do you use for setting priorities?

Dr. KIRSCHSTEIN. Under the assignment guidelines of the Division of Research Grants, NIH, investigator-initiated grant applications are assigned to the National Institute of General Medical Sciences if they are so basic that they are relevant to two or more categorical institutes. Priority for funding of applications assigned to the National Institute of General Medical Sciences is given on the basis of several considerations; the encouragement of this committee and the Congress, administration plans, and the scientifically most meritorious, as judged by peer review-study sections.

Mr. MICHEL. What determines which areas will get the most attention?

Dr. KIRSCHSTEIN. Insofar as priorities are set on scientific grounds they are determined by scientific opportunity and merit.

SUPPLEMENTAL RESEARCH

Mr. MICHEL. Could you provide us with a listing of the activities within general medical that supplement research done in the other research in terms of specific programs? Do your activities supplement all the other institutes or just certain areas of concentration?

Dr. KIRSCHSTEIN. The research supported by National Institute of General Medical Sciences is not supplementary but basic to that of

the other institutes. Thus the cellular and molecular basis of disease program supports work throughout the country that is likely to become relevant to the missions of all the other institutes. Similarly with the genetics program.

Our pharmacology-toxicology program includes support of activities conducted within research centers, where a number of investigators benefit from collaboration, mutual exchanges, and shared equiptors benefit from collaboration, mutual exchanges, and shared equipment and other resources. Individual projects in these centers may well have a categorical thrust, but the general scientific theme of the centers is multicategorical and focused on general principles. The categorical pharmacological research done with pharmacology-toxicology research centers and that done under individual research grants from other institutes complement each other in the sense that the former is done from the point of view of generalizable pharmacological principles, the other with a particular clinical condition in mind.

Mr. MICHEL. Obviously, we can't research every single possible area and disease in massive detail. In general research, how do you decide which leads seem to be the most promising and should be followed up?

Dr. KIRSCHSTEIN. The scientist-grantees' attention shifts from time to time as new discoveries and methods open new opportunities for research that appear promising. This is automatically reflected in greater numbers of meritorious applications in these general areas, which in turn is reflected in a greater proportion of grants funded in this area. The assumption underlying this way of deciding is that the scientific community is in the best position to select those projects which are most likely to pay off scientifically at any one time. We believe this is also the most economical approach to funding priorities in basic research.

Mr. MICHEL. Thank you.

Mr. FLOOD. Mr. Conte.

COOPERATION WITH HSA

Mr. CONTE. Dr. Kirschstein, would you tell us what cooperative efforts have been instituted during the past year between trauma centers and the emergency medical systems supported by the Health Services Administration?

Dr. KIRSCHSTEIN. There are currently nine trauma and burn research centers supported by the National Institute of General Medical Sciences. Six of these are located in cities or States which are developing emergency systems through support obtained from the emergency medical systems program of the Health Services Administration. In these communities, the hospitals which have trauma research centers have been designated as the emergency hospitals and receive most of the accident victims. Such accessibility provides more patients for study but more importantly permits these patients to benefit from the knowledge already accrued from on-going research. The clinicians responsible to the research centers in some instances have established close liaison with the emergency room staff and have participated in the training of paramedicals who man the ambulances.

ADEQUACY OF BUDGET

Mr. CONTE. Do you feel that the amount of money being requested for this year's National Institute of General Medical Sciences budget will adequately meet your research needs?

Dr. KIRSCHSTEIN. The amount of money being requested will enable our institute to fund only a very small number of new and competing research grants.

Mr. CONTE. Do you feel the sum requested is disproportionate to the budgets of other institutes in terms of meeting those needs?

Dr. KIRSCHSTEIN. The sums requested for the National Institute of General Medical Sciences are not disproportionate to those of other institutes in terms of meeting our needs.

Mr. CONTE. Will your programs be adversely affected by the much larger sums being requested for the Cancer and Heart Institute?

Dr. KIRSCHSTEIN. Our programs will not be adversely affected by the Cancer and Heart Institute budgets but we will not, within our budget, be able to have many new research grants.

RESEARCH INTERACTION WITH OTHER INSTITUTES

Mr. CONTE. Would you outline the areas in which you have research programs which interact with the programs of some of the other institutes?

Dr. KIRSCHSTEIN. Many of the National Institute of General Medical Sciences programs interact with the programs of other Institutes. In general, the National Institute of General Medical Sciences supports basic research activities which, when they appear to develop more toward the goals of the categorical, disease-oriented Institutes, are then supported by them. Thus there is complementation but little, if any, duplication. The areas where we cooperate are in genetics where much of the research effort which impinged on cardiovascular disease, inherited blood diseases and cystic fibrosis is subsequently supported by the National Heart and Lung Institute; inherited metabolic diseases by the National Institute of Arthritis, Metabolism and Disgestive Diseases; in the basic genetics of neural disorders which complement studies by the National Institute of Neurological and Communicative Disorders and Stroke; and in developmental genetics which is coordinated with the programs of the National Institute of Child Health and Human Development.

Mr. CONTE. Is there duplication of effort involved here, for example in your molecular genetics research, some of which is conducted at the Cancer Institute also?

Dr. KIRSCHSTEIN. Basic molecular genetics research is heavily supported by the National Institute of General Medical Sciences. When such efforts become specifically relevant to one of the Institutes such as the National Cancer Institute, coordination occurs. An example is a study supported by the National Institute of General Medical Sciences concerning the genetic predisposition to develop lung cancer. After the initial observation, the National Cancer Institute has taken over the major role in this work and we are coordinating our efforts.

Mr. CONTE. Would you go into detail about several of your research efforts which affect the work of the other Institutes?

Dr. KIRSCHSTEIN. The Boston collaborative drug surveillance program is currently supported by an interagency agreement between the National Institute of General Medical Sciences and the Food and Drug Administration. This is the most important drug surveillance unit in the United States and it has been supported by the National Institute of General Medical Sciences since 1967. This unit has provided leads for clinical research currently undertaken by the National Cancer Institute and the National Heart and Lung Institute. The National Institute of General Medical Sciences research on cell membranes and their role in cell recognition has a vital role in leading to an understanding of the formation of body organs during early stages of development, National Institute of Child Health and Human Development; in the escape of cells from organized control to form cancer, National Cancer Institute; and in the causation of immune disease, National Institute of Allergy and Infectious Diseases. The role of membranes in nerve conduction and in the control of molecules entering and leaving the cell is vital to the research of the National Institute of Neurological and Communicative Disorders and Stroke and to the National Institute of Arthritis, Metabolism, and Digestive Diseases in work on the mode of action of hormones, and on renal and disgestive disease.

The National Institute of General Medical Sciences supported work on familial hypercholesterolemia and genetic variation to susceptibility to lung cancer, affecting the program interests of the National Heart and Lung Institute and the National Cancer Institute, have already been cited.

One of the many projects in a genetics center is a study of the genetics of refractive errors. Although the study is not complete, preliminary results indicate that poor eyesight is often inherited, and is more frequent in certain ethnic groups than in others. This work is clearly of interest to the National Eye Institute. One of the projects at another genetics center is a study of hereditary deafness, a project that relates to the mission of the National Institute of Neurological and Communicative Disorders and Stroke.

GENETIC ENGINEERING RESEARCH

Mr. CONTE. Do you feel that the concern about the techniques in genetic engineering research will lead to a need for Federal legislation to insure the licensing and approval of all laboratories where such research is conducted?

Dr. KIRSCHSTEIN. There is adequate concern by the scientific community, and the consultants and science administrators of the National Institutes of Health that no improper or unsafe experimentation be done. We believe, basically, that a self-policed honor system will work and that Federal licensing would be difficult to enforce, and would most likely not be effective, particularly since it could not apply to other countries.

NEW GUIDELINES

Mr. CONTE. Do you think that the guidelines being proposed by the National Institutes of Health Recombinant DNA Molecule Program Advisory Committee will produce any serious handicaps in arriving

at sufficient laboratory facilities in universities which can safely conduct such research?

Dr. KIRSCHSTEIN. The range of potential biohazards is currently being defined by this committee. Probably, most experiments will present only low hazards and can be performed using appropriately disarmed biological vectors, currently under development, and appropriate enclosures, such as special hoods. The latter are of relatively low cost. Since the number of laboratories involved in such work is, as yet limited, the costs involved would, at this time, not be substantial. A limited amount of experimentation will involve substantially greater biohazards. It is likely that a more thorough review, possibly at the level of a National Institutes of Health review committee, would be required in these cases. It may be recommended that this class of research can only be carried out under conditions of biological containment now used for extremely dangerous agents.

NEW LEGISLATIVE ACTION

Mr. CONTE. What additional legislative action, if any, do you think might be desirable to cope with this problem in new genetics research?

Dr. KIRSCHSTEIN. At this stage we do not think additional legislative action is necessary.

RESEARCH OVERLAP WITH NCI

Mr. CONTE. How much of the molecular genetic and other research conducted under your Institute's authority overlaps with research being conducted by the National Cancer Institute?

Dr. KIRSCHSTEIN. It is difficult to determine how much research in a certain area supported by the National Institute of General Medical Sciences is also potentially within the mission of other Institutes particularly the National Cancer Institute. In any given field, such as molecular genetics, the research we sponsor will be relevant to two or more Institutes or such that cannot be related to any other Institute while research in a field such as this supported by the National Cancer Institute will be related to their mission.

RELATIONSHIP WITH NCI

Mr. CONTE. What is your relationship to the Cancer Institute in terms of funding and research liaison?

Dr. KIRSCHSTEIN. In those cases where it is difficult to determine who should sponsor the research, dual assignments are made in which case the application may be funded by either Institute but not by both.

NEW GENETIC CENTERS

Mr. CONTE. You have reported that there are now 10 genetics centers in operation. Where are they located? What do they do? Are they accessible to the general public?

Dr. KIRSCHSTEIN. The 10 centers are located at: the University of Washington, Seattle, Wash.; the University of California, San Diego, Calif.; Albert Einstein College of Medicine, Bronx, N.Y.; Mt. Sinai

School of Medicine, New York, N.Y.; Johns Hopkins University Medical Schools, Baltimore, Md.; University of Texas, Houston, Tex.; University of California, San Francisco, Calif.; Yale University, New Haven, Conn.; University of Pennsylvania, Philadelphia, Pa.; and Indiana University, Indianapolis, Ind. The centers involved in genetic community services, including genetic counseling and amniocentesis, although only research components are funded, such service activities provide abundant material for investigation and a setting in which the newest research findings can best be clinically evaluated. The basic scientists are provided with an environment that stresses the potential relevance of their work to human health needs.

The research conducted at the centers is as accessible to the public as far as the limited staff and the other duties of a busy laboratory permit. However, the benefits of the center to the community in which they are embedded are great. All of the centers provide genetic services, including genetic counseling and diagnostic tests, such as amniocentesis. Although such services are not funded directly under the genetic centers grant mechanism, it is generally recognized that optimum genetic services can only be provided when backed up by an atmosphere of excellence in research. By creating the necessary research environment, the centers not only support the societal effort of advancing knowledge of genetic disease, but the community goal of improved clinical services. The genetic centers were conceived as means to support collaborative research that would not otherwise be possible and to translate advances in basic genetics to clinical application.

Mr. CONTE. Are there plans for new facilities of this type in this year's budget?

Dr. KIRSCHSTEIN. At the present time, there are no plans for a substantial increase in the number of National Institute of General Medical Sciences genetic centers. We are satisfied that the National Institute of General Medical Sciences genetics program has achieved a reasonable balance between the support of individual projects, and the larger projects, such as centers, which were initiated for special purposes not possible with other funding instruments.

GENETIC COUNSELING AND SCREENING

Mr. CONTE. Do you encourage genetic counseling and screening programs?

Dr. KIRSCHSTEIN. All of the genetic centers whose research is supported by the National Institute of General Medical Sciences provide medical genetics services, including counseling. Several are engaged in screening programs.

Mr. CONTE. How do you go about this work?

Dr. KIRSCHSTEIN. Patients are referred from pediatricians and other physicians to genetic clinics related to the centers.

ACCOMPLISHMENTS OF AUTOMATED CLINICAL LABORATORY PROGRAM

Mr. CONTE. What have you accomplished in your automated clinical laboratory program during the past year?

Dr. KIRSCHSTEIN. We have moved ahead with the development of additional standard reference materials, now 18 in all, in collab-

oration with the National Bureau of Standards. These standards allow laboratories to calibrate their analytical methods and instruments more accurately. They are also being used by the communicable disease center in their proficiency testing programs for clinical laboratories.

We have developed miniaturized instrumentation for the rapid and more reliable determination of clinical laboratory procedures, for example GeMSAEC—the fast clinical analyzer.

We have continued, with considerable success in this past year, the development of a positive patient and sample identification system which will, with further elaboration, insure that the results of chemistry tests on a particular patient will be positively identified with the patient. The elimination of mistaken identity and false reporting of results will be an important step forward.

We have arranged, and are about to hold in May 1975, a National Conference on the Utilization of Laboratory Tests. At present, the practice of using a screening battery of tests has become commonplace and the number of tests being ordered each day is on the increase. The proponents of such screening techniques claim that they are an effective method for the early detection and monitoring of disease. Other equally qualified scientists are critical of such testing, claiming that there is very little hard evidence that they improve morbidity or mortality. Individuals knowledgeable in this field will be invited to the conference to discuss the situation and make recommendations with respect to it.

Mr. CONTE. What are your future plans for this program?

Dr. KIRSCHSTEIN. Future plans for this program include the development of: More accurate and direct methods for the determination of chemicals in the blood; more rapid and accurate methods for the assay of enzymes and hormones; positive specimen identification and automatic accessioning of biological samples as they appear in laboratory receiving offices; automated cytology techniques; more rapid, economical, and specific viral diagnostic procedures; a more precise elaboration of "normal values" for procedures conducted in the clinical laboratory; and additional mechanized and automated analytical instruments, devices, and systems for the clinical laboratory.

COMPUTER DIAGNOSIS

Mr. CONTE. What is the status of computer diagnosis?

Dr. KIRSCHSTEIN. Effective differential medical diagnosis by computer remains in a primitive stage.

SPACE PROGRAM TECHNIQUES

Mr. CONTE. What are some of the new techniques utilized by automated clinical laboratories which have been spinoffs from our space program?

Dr. KIRSCHSTEIN. Minicomputers; ultra-micro-instrumentation developed in the space program has been responsible for the appearance of very small—space-saving and highly reliable computers in the clinical laboratory. They are now being used in combination with a variety of instruments.

Integrated circuit technology: This technology, solid state, microchip, is now used in the heads of several instruments. It provides for more precise and reliable instrumentation readout.

COORDINATION WITH NASA

Mr. CONTE. Are any of your medical service programs coordinated with the National Aeronautics and Space Administration's remote health care facilities program?

Dr. KIRSCHSTEIN. We have no formal coordination with the National Aeronautics and Space Administration, however, we interact informally and continuously with those various aspects of the National Aeronautics and Space Administration biomedical research and development program that are germane to our programmatic responsibilities.

USE OF TELEMETRIC EXAMINATION

Mr. CONTE. Are there any programs underway or under consideration to utilize telemetric examination of patients in remote areas?

Dr. KIRSCHSTEIN. We are currently supporting a promising development of instrumentation for long-range transmission of X-ray images, which may allow remote areas in the country to have benefit of expert consultation from medical centers.

Mr. CONTE. Would you have access to the National Aeronautics and Space Administration ATS–6 satellite on an experimental basis for such a program?

Dr. KIRSCHSTEIN. We could have access to this satellite but it is not pertinent to our programmatic activities at this time.

Mr. CONTE. Are any of the programs for which you are requesting funding being funded on a multiyear funding basis? Would you provide a listing for the record if this is the case?

Dr. KIRSCHSTEIN. There are none.

PHARMACOLOGY-TOXICOLOGY PROGRAM

Mr. CONTE. Would you elaborate on your pharmacology-toxicology program?

Dr. KIRSCHSTEIN. The pharmacology-toxicology program is a broadly based effort with continuing commitments ranging from the most basic synthetic chemistry, molecular and biochemical pharmacology, and toxicology to drug development and clinical studies. The first goal of the program is to continue to seek excellence and advancement in all of these interdependent areas.

Mr. CONTE. On what are you focusing this program this year?

Dr. KIRSCHSTEIN. A current assessment of the field indicates that several areas are severely underdeveloped in terms of the immediate and future needs of this country's health. Departments of pharmacology and medicine throughout the country are actively trying to recruit well-trained clinical pharmacologists. Because of the shortage of personnel, clinical pharmacological research needs further intensive development. For this reason, the National Institute of General Medical Sciences selected clinical pharmacology as the only pharmacological

area in which postdoctoral institutional fellowship applications would be solicited for fiscal year 1975.

ACUPUNCTURE

Mr. CONTE. Are you conducting investigations of acupuncture in your anesthesiology program?

Dr. KIRSCHSTEIN. The National Institute of General Medical Sciences currently supports six projects on acupuncture in the amount of $144,924 direct costs. These studies attempt to establish the acupuncture points and compare the effectiveness of acupuncture to conventional methods in the areas of skin sensation, analgesia in acute surgical procedures, the management of chronic pain, and asthma.

Mr. CONTE. Thank you.

Mr. FLOOD. Thank you, Dr. Kirschstein.

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

For expenses, not otherwise provided for, necessary to carry out title IV, part E and I of the Public Health Service Act with respect to general medical sciences, [$187,400,000]. *$161,630,000*

For "National Institute of General Medical Sciences" for the period July 1, 1976, through September 30, 1976, $40,295,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Amounts Available for Obligation

	1975 Estimate 1/	1976 Estimate
Appropriation	$187,400,000	$161,630,000
Comparative transfers to:		
"Research Resources" (For the Rhesus Monkey Supply Program)	-22,000	---
"Office of the Director" ($30,000 for Public Affairs Reorganization, $58,000 for transfer of the Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	-88,000	---
Total, obligations	187,290,000	161,630,000

1/ Excludes 1973 restorations in the amount of $2,524,445.

Summary of Changes

1975 Estimated obligations	$187,290,000
1976 Estimated obligations	161,630,000
Net change	-25,660,000

	1975 Pos.	1975 Amount	Change from 1975 Pos.	Change from 1975 Amount
Increases:				
A. Built-in:				
1. Within-grade pay increase cost...	---	---	---	+$32,000
2. Extra day of pay in F.Y. 1976....	---	---	---	+13,000
3. FTS rate increase.....	---	---	---	+12,000
4. Postage increase.....	---	---	---	+2,000
5. Annualization cost of October, 1974 pay raise.....	---	---	---	+199,000
6. Increased costs for General Expense and Program Evaluation.	---	---	---	+613,000
7. Miscellaneous operating costs....	---	---	---	+385,000
Subtotal.....	---	---	---	+1,256,000
B. Program:				
1. Research Grants:				
a. Noncompeting continuations...	---	$64,796,000	---	+7,204,000
2. Special programs.....	---	15,621,000	---	+9,147,000
3. Fellowships:				
a. Noncompeting	---	3,927,000	---	+723,000
4. Training Grants:				
a. Supplemental.....	---	---	---	+4,000
Subtotal.....	---	---	---	+17,078,000
Total, increases.....	---	---	---	+18,334,000
Decreases:				
A. Built-in:				
1. Payment to "NIH Management Fund" for centrally furnished services.....	---	---	---	-132,000
B. Program:				
1. Research Grants:				
a. Competing renewals.....	---	28,420,000	---	-22,173,000
2. Special programs.....	---	16,022,000	---	-8,953,000
3. Fellowships:				
a. Competing.....	---	12,239,000	---	-11,389,000
4. Training Grants:				
a. Noncompeting.....	---	35,701,000	---	-354,000
5. Research and Development Contracts.....	---	3,993,000	---	-993,000
Subtotal.....	---	---	---	-43,862,000
Total, decreases.....	---	---	---	-43,994,000
Total, net change.....	---	---	---	-25,660,000

Explanation of Changes

Increases:

A. Built-in:

1. The total built-in increase of $1,256,000 included in Research Management and Program Services will provide: $32,000 for within-grade pay increases in 1976; $13,000 for an extra day's pay in 1976; $12,000 for increased cost of using the Federal Telecommunications System; $2,000 for postage increase; $195,000 for the Research Management and Program Services portion of the October 1974 pay raise annualization cost; $4,000 for the Pharmacology-Toxicology direct training program portion of the October 1974 pay raise annualization cost; $613,000 for increased costs in General Expense and Program Evaluation; and $385,000 for increased operating costs.

B. Program:

1. The total program increase of $17,078,000 will provide: $7,204,000 for noncompeting continuations, regular research grants; $9,147,000 for Special Programs, of which $2,107,000 is for Pharmacology-Toxicology Research Centers; $614,000 is for Biomedical Engineering Research Centers; $543,000 is for Diagnostic Radiology Research Centers; $442,000 is for Anesthesiology Research Centers; $1,815,000 is for Trauma and Burn Research Centers; $2,316,000 is for Genetic Research Centers; $1,200,000 is for Molecular Pathology Research Centers; $110,000 is for Scientific Evaluation; $723,000 for noncompeting fellowships; and $4,000 is for supplemental training grants.

Decreases:

A. Built-in:

1. The built-in decrease provides $132,000 for payment to the "NIH Management Fund" for centrally furnished services.

B. Program:

1. The total program decrease of $43,862,000 will provide: $22,173,000 for competing renewals, regular research grants; $8,953,000 for Special Programs, of which $1,292,000 is for Pharmacology-Toxicology Research Centers; $515,000 is for Diagnostic Radiology Research Centers; $493,000 is for Biomedical Engineering Research Centers; $280,000 is for Anesthesiology Research Centers; $1,815,000 is for Trauma and Burn Research Centers; $2,497,000 is for Genetic Research Centers; $500,000 is for Molecular Pathology Research Centers; $1,561,000 is for Research Career Program; $11,389,000 for competing fellowships; $354,000 for noncompeting training grants; and $993,000 is for Research and Development Contracts.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
19	Pharmacology-Toxicology.....	---	$27,756,000	---	$25,571,000	---	-$2,185,000
22	Biomedical Engineering.....	---	20,428,000	---	18,249,000	---	-2,179,000
25	Clinical and Physiological Sciences.....	---	21,008,000	---	19,393,000	---	-1,615,000
28	Genetics.....	---	51,205,000	---	42,483,000	---	-8,722,000
31	Cellular and Molecular Basis of Disease.....	---	60,766,000	---	48,687,000	---	-12,079,000
34	Research Management and Program Services.	155	6,127,000	152	7,247,000	-3	+1,120,000
	Total obligations..	155	187,290,000	152	161,630,000	-3	-25,660,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	155	152	-3
Full-time equivalent of all other positions	5	5	-0-
Average number of all employees	160	154	-6
Personnel compensation:			
Permanent positions	$2,582,000	$2,697,000	+$115,000
Positions other than permanent	110,000	110,000	-0-
Other personnel compensation	98,000	99,000	+1,000
Subtotal, personnel compensation	2,790,000	2,906,000	+116,000
Personnel benefits	434,000	562,000	+128,000
Travel and transportion of persons	155,000	100,000	-55,000
Transportation of things	20,000	34,000	+14,000
Rent, communications, and utilities	95,000	309,000	+214,000
Printing and reproduction	41,000	175,000	+134,000
Other services:			
Project contracts	3,993,000	3,000,000	-993,000
Payment to NIH Management Fund	1,905,000	1,773,000	-132,000
Other	1,003,000	1,704,000	+701,000
Supplies and materials	76,000	79,000	+3,000
Equipment	52,000	53,000	+1,000
Grants, subsidies, and contributions	176,726,000	150,935,000	-25,791,000
Total obligations by object	187,290,000	161,630,000	-25,660,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1975 House Report	
Trauma	
1. The committee will expect a report on the role played by these trauma centers in the new Emergency Medical System being developed by the Health Services Administration (page 36).	1. We are in close contact with the Director of the Emergency Medical Services System (EMS) and have integrated our programs so that several EMS programs are being established in the institutions which currently have NIGMS trauma research centers, e.g. at the University of Washington, Seattle. We are also developing and programming trauma research centers in institutions which have ongoing EMS programs, e.g. at the University of California, San Diego. Currently, there are combined programs at SUNY, Buffalo, and University of California, San Francisco. The combined programs share their experience and technology with the neighboring communities and serve as models and demonstration units.
MARC Program	
1. The goal of the MARC (Minority Access to Research Careers) Program is to attract and prepare minority students--not only black but Mexican-Americans, American Indians, etc.--for careers in the health sciences. The Committee finds this program worthwhile and commendable and expects that it will be maintained (page 37).	1. We have extended our efforts in an attempt to reach all minority group students, including the Mexican-Americans and the American Indians, by direct contact with these minority group institutions. We have provided support for two Mexican-American faculty members via the MARC Faculty Fellowship. We expect as a result of our efforts to receive additional applications for training.
1975 Senate Report	
Cellular and Molecular Basis of Disease	
1. The committee encourages new work and initiatives in this area (page 56).	1. We intend to continue to give emphasis to multidisciplinary and collaborative research and research training efforts between pathologists and basic scientists toward the understanding of the human cell in biochemical and molecular terms. It is expected that at least one additional Research Center will be funded.

1975 Senate Report (continued)

Genetics	
1. The Committee further notes that support has been awarded to two new genetic research centers, for important studies on hereditary deafness and congenital heart defects and for needed studies on the social, legal, and ethical issues attending the advance of genetic medicine. The Committee encourages further expansion of this effort (page 57).	1. Our present Genetics Program, including the research centers, encompasses the best scientists in the field and a broad range of research interests, and is widely distributed geographically. We have supported a workshop on methods for the evaluation of genetic counseling which relates to the social, legal, and ethical issues.
Burn Research	
1. The Committee recommends that the NIGMS continue with an active program in this area and concentrate on the establishment of a limited number of Burn-trauma Centers with the additional funds provided (page 57).	1. As a result of active programming, we have activated one burn research center, have received two new applications for June Council, and may receive three or four more. The majority of the currently active trauma research centers devote a considerable portion of their resources to burn research. In addition, several new project grants for in-depth studies of the burn problem have been activated.
Biomedical Engineering	
1. Following the Committee's urging the Institute initiated a Biomedical Engineering Research Centers Program. The Committee encourages the expansion of this program within the funds provided by Congress (page 58).	1. To-date, Biomedical Engineering Research Centers have been established at Stanford University and at the University of Washington. Currently, the establishment of three new centers in F.Y. 1975 and F.Y. 1976 is under consideration. Over the next several years, we expect to fund an additional three to four centers. As anticipated, these centers will cover a broad spectrum of basic and applied biomedical engineering research activities.
Medical Scientist Training Program	
1. The Committee commends the Institute for the development of the innovative Medical Scientist Training Program, which combines medical and scientific training for 350 outstanding students in 12 of the Nation's leading medical schools. The Committee recognizes the possibilities for this program and encourages the Institute to expand the program to other schools (page 58).	1. Two new Medical Scientist Training Programs were established in F.Y. 1975 using released impounded funds. Under the authority of the National Research Act, we have received applications for additional awards for medical scientist training, and we expect to fund five to seven additional programs.

1975 Senate Report (continued)

MARC Program

1. The Committee is extremely distressed to note that the President's Budget request for the MARC program has been slashed from a 1974 obligation level of $4,019,000 to $107,000 for F.Y. 1975. Moreover, on August 12, 1974, the Department indicated that within the House Allowance, no more than $750,000 will be used for the MARC program--a decrease of $3.2 million below last year's level. The Committee cannot agree with these priorities and recommends that within the amount provided by the Congress, the MARC program should be maintained at last year's level (page 58).

1. Within the authority available under the National Research Service Act of 1974, this program intends to continue and expand its fellowship and training activities. We expect to receive and fund 25-50 fellowship applications and are currently funding seven predoctoral training grants.

Training

1. The Committee directs the NIGMS to continue its support of training at the predoctoral level. The Committee is very concerned over the issue of training in general and instructs the Institute that, as nearly as possible within the level of funds provided, all training programs should be reinstated and operate as they have in the past (page 59).

1. The Institute is continuing the orderly phase-out of the old training programs. Regulations have been published in the Federal Register for training awards under the new National Research Service Award Act. Requests for training applications have also been sent out--including institutional awards and pre- and post-doctoral training, and the Institute has been authorized to fund these types of grants in 1975.

Authorizing Legislation

Legislation	1976 Authorized	1976 Appropriation requested
Public Health Service Act Section 301—Grants programs.....	Indefinite	
Title IV, Part E, Institutes of Child Health and Human Development and of General Medical Sciences.....	Indefinite	$158,699,000 2/
Title IV, Part I - National Research Service Awards Act.....1/.		2,931,000 2/

1/ Authorization expires June 30, 1975; extension legislation is proposed.

2/ Funding estimate only.

National Institute of General Medical Sciences

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$119,232,000	$119,232,000	$123,318,000	$121,799,000
1967	130,781,000	136,062,000	138,562,000	138,562,000
1968	151,941,000	151,941,000	154,430,000	151,927,000
1969	157,540,000	153,013,000	158,013,000	155,276,500
1970	146,051,000	146,051,000	166,061,000	156,407,000
1971	142,218,000	158,002,000	163,002,000	158,002,000
1972	143,763,000	161,254,000	171,254,000	166,277,000
1973	167,107,000	173,655,000	196,484,000	173,855,000 1/
1974	136,929,000	174,144,000	181,886,000	166,805,000 2/
1975	168,219,000	177,998,000 3/	197,890,000	187,290,000
1976	161,630,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction,

3/ Excludes Research & Development Contracts which were not considered by the House due to lacking authorization.

National Institute of General Medical Sciences

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$124,538,000	$124,538,000	$129,388,000	$127,188,000
1967	137,175,000	142,613,000	145,113,000	145,113,000
1968	160,284,000	160,284,000	164,284,000	160,284,000
1969	165,777,000	161,250,000	166,250,000	163,513,500
1970	154,288,000	154,288,000	175,000,000	164,644,300
1971	148,376,000	166,072,000	171,072,000	166,072,000
1972	150,400,000	168,490,000	179,318,000	173,474,000
1973	175,960,000	183,171,000	206,000,000	183,171,000 1/
1974	138,573,000	175,778,000	183,500,000	168,329,000 2/
1975	168,329,000	178,108,000 3/	198,000,000	187,400,000
1976	161,630,000			

1/ Note: This appropriation authority was the continuing resolution. The appropriation amount was the House allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes Research & Development Contracts which were not considered by the House due to lacking authorization.

Justification

National Institute of General Medical Sciences

Authorizing Legislation: Public Health Service Act, Title IV, Part E

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	155	$3,224,000	152	$3,468,000	-3	+$244,000
Other expenses.....	---	184,066,000	---	158,162,000	---	-25,904,000
Total.....	155	187,290,000	152	161,630,000	-3	-25,660,000

General Statement

The National Institute of General Medical Sciences supports research and research training in the general or basic biomedical sciences which have significance for two or more institutes or are outside the general area of responsibility of any other institute.

Institute activities are organized and conducted through its five operating programs: Pharmacology-Toxicology, Biomedical Engineering, Clinical and Physiological Sciences, Genetics, and Cellular and Molecular Basis of Disease. Interprogram cooperation is stressed because projects and developments in one program frequently are relevant and of consequence to others. Each program fosters and supports multidisciplinary approaches and resources.

Programmed research objectives are to elucidate the genetic, molecular, and cellular bases for diseases, to enable the use of safer and more effective drugs, to discover better ways for treatment of accident victims, and through the application of engineering approaches and manpower, to develop more rational automated laboratory procedures and techniques for use in health care delivery. The National Institute of General Medical Sciences also has principal responsibility for supporting, through predoctoral training programs, young medical research scientists in a number of basic science disciplines. This support is also provided in scientific areas closely related to several clinical disciplines through postdoctoral individual fellowship awards. In addition, special support is given to increase access of blacks and members of other minority groups to careers in biomedical research and academic medicine through the minority access to research careers (MARC) training program.

The National Institute of General Medical Sciences is requesting a total of $161,630,000.

DHEW - National Institutes of Health

Crosswalk - F.Y. 1975 Column of F.Y. 1976 President's Budget

INSTITUTE: National Institute of General Medical Sciences

(Dollars in Thousands)

Program	Research Grants						Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Special		Training Programs				
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships			
1. Pharmacology-Toxicology.....	$8,222	$3,390	$6,500	$904	$3,144	$2,876	$2,276	$444	$27,756
2. Biomedical Engineering.....	6,428	4,142	3,051	494	3,783	1,252	1,278	---	20,428
3. Clinical & Physiological Sciences.....	2,376	1,187	8,228	347	8,120	750	---	---	21,008
4. Genetics.....	23,908	10,074	6,681	2,590	2,600	4,913	439	---	51,205
5. Cellular & Molecular Basis of Disease.....	23,862	9,627	500	2,348	18,054	6,375	---	---	60,766
6. Research Management & Program Services.....	---	---	---	---	---	---	---	6,127	6,127
Total obligations.....	64,796	28,420	24,960	6,683	35,701	16,166	3,993	6,571	187,290

DHEW - National Institutes of Health

Crosswalk - F.Y. 1976 Column of F.Y. 1976 President's Budget

INSTITUTE: National Institute of General Medical Sciences

(Dollars in Thousands)

Mechanism / Program	Research Grants						Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Special		Training Programs				
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships			
1. Pharmacology-Toxicology....	$10,022	$703	$7,315	$714	$3,144	$1,308	$1,917	$448	$25,571
2. Biomedical Engineering.....	8,729	882	3,200	457	3,783	267	931	---	18,249
3. Clinical & Physiological Sciences.....	2,209	247	8,390	264	8,120	163	---	---	19,393
4. Genetics.....	27,131	2,447	6,500	1,973	2,600	1,680	152	---	42,483
5. Cellular & Molecular Basis of Disease.....	23,909	1,968	1,200	1,824	17,704	2,082	---	---	48,687
6. Research Management & Program Services.....	---	---	---	---	---	---	---	7,247	7,247
Total obligations.....	72,000	6,247	26,605	5,232	35,351	5,500	3,000	7,695	161,630

National Institute of General Medical Sciences

Budget Mechanism

	1975*			1976		
	Number	FTE 1/	Amount	Number	FTE 1/	Amount
Research Grants:						
Regular:						
Non-competing.....	910		$64,796,000	1,144		$72,000,000
Competing.....	428		16,959,000	67		3,295,000
New.....	186		10,484,000	50		2,355,000
Supplemental.....	(45)		977,000	(30)		597,000
Subtotal.....	1,524		93,216,000	1,261		78,247,000
Special:						
Pharmacology-Toxicology Research Centers.....	11		6,500,000	13		7,315,000
Diagnostic Radiology Research Centers...	2		972,000	2		1,000,000
Biomedical Engineering Research Centers.....	6		2,079,000	6		2,200,000
Anesthesiology Research Centers...	5		3,028,000	6		3,190,000
Trauma and Burn Research Centers...	16		5,200,000	15		5,200,000
Genetic Research Centers.....	9		6,681,000	10		6,500,000
Molecular Pathology Research Centers...	1		500,000	2		1,200,000
Research Career Programs.....	255		6,277,000	190		4,716,000
Scientific Evaluation	---		406,000	---		516,000
Subtotal.....	305		31,643,000	244		31,837,000
Total Research Grants....	1,829		124,859,000	1,505		110,084,000
Fellowships:						
Noncompeting.....	175		3,927,000	102		4,650,000
Competing.....	---		---	---		---
New.....	471		12,239,000	30		850,000
Supplemental.....	---		---	---		---
Subtotal.....	646	770	16,166,000	132	280	5,500,000
Training Grants:						
Noncompeting.....	409		35,701,000	289		35,347,000
Competing.....	---		---	---		---
New.....	---		---	---		---
Supplemental.....	---		---	---		4,000
Subtotal.....	409	4,058	35,701,000	289	4,058	35,351,000
Total, Grants.....	2,884		176,726,000	1,926		150,935,000
Research & Development Contracts.....	12		3,993,000	9		3,000,000
Research Management and Program Services.....	---		6,571,000	---		7,695,000
TOTAL.....	2,896		187,290,000	1,935		161,630,000

* Excludes 1973 appropriation restorations.
1/ Full time equivalents.

Pharmacology-Toxicology

Authorizing Legislation: Public Health Service Act, Title IV, Part E

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits.....	---	---	---	---	---	---
Other expenses.....		$27,756,000		$25,571,000		-$2,185,000
Total.....		27,756,000		25,571,000		-2,185,000
Budget Mechanism:						
Research Grants:						
Regular program:						
Noncompeting.....	139	8,222,000	176	10,022,000	+37	+1,800,000
Competing.....	65	3,390,000	17	703,000	-48	-2,687,000
Subtotal Regular	204	11,612,000	193	10,725,000	-11	-887,000
Special programs:						
Pharmacology-Toxicology Research Centers.....	11	6,500,000	13	7,315,000	+2	+815,000
Research Career...	33	802,000	23	604,000	-10	-198,000
Scientific Evaluation.....	---	102,000	---	110,000	-0-	+8,000
Subtotal Special	44	7,404,000	36	8,029,000	-8	+625,000
Fellowships 1/.....	147	2,876,000	84	1,308,000	-63	-1,568,000
Training Grants 1/..	357	3,144,000	357	3,144,000	-0-	-0-
Research & Development Contracts....	5	2,276,000	4	1,917,000	-1	-359,000
Research Management & Program Services.	---	444,000	---	448,000	-0-	+4,000
Total.....		27,756,000		25,571,000		-2,185,000

1/ Numbers reflect full time equivalent.

Program Plans in F.Y. 1976

Several research areas in the Pharmacology-Toxicology Program offer promising opportunities for progress, including pharmacogenetics, immunopharmacology, and dermatopharmacology. In addition to learning how the metabolism of a drug may vary from individual to individual on the basis of genetic differences, followup studies on how to detect and how to deal with these differences are essential. Inherited differences in drug metabolism offer a promising tool for discovering the site of action of drugs and the pathogenesis of the various conditions in which they are effective. Many of these opportunities in pharmacogenetics are the result of recent advances in fundamental genetics supported by another program in this Institute. As the field of immunology has become increasingly important in medicine, particularly in relation to the control of cancer and the rejection of transplanted organs, the need for better pharmacologic tools to control immunologic mechanisms has become very great indeed.

At birth, a child faces a tremendous challenge--especially if premature--in suddenly having to rely on its own means for detoxifying drugs and other substances. An example of such a challenge is seen in the child whose blood has an Rh factor incompatibility with the mother. In these children, a harmful level of a blood pigment, bilirubin, builds up quickly after birth. In order to predict accurately whether there is danger of brain damage and thus the urgent need for an exchange transfusion, it is important to know how much of this pigment is in a form (unbound to blood protein) that can enter the brain. One of the Institute's grantees is now making progress in developing a rapid, reliable, and practical test method for detection of unbound bilirubin. Since aspirin is among the several drugs that affect the fraction that is bound, and this is such a commonly used drug, this problem is not a trivial one. It should be possible to lower the incidence of brain death by relying on determinations of this kind.

Another promising finding has been the development of a better method to visualize the heart in order to demonstrate the presence and size of injury in victims of heart attacks. Using a new compound carrying a radioactive label whose activity can be detected through the intact chest wall and special radiologic cameras, a diagnosis may be possible within as short a time as 5 to 10 minutes. A further valuable feature of this compound is its short half-life of radioactivity, which allows repeat examinations on a daily basis.

The Institute is continuing its support of the Boston Collaborative Drug Surveillance Program, now in collaboration with the Food and Drug Administration through an interagency agreement. This program has already proven productive in identifying a number of associations between drugs and undesirable side effects--associations which would not otherwise have been detected, at least not in such a short time. Another interagency agreement has been arranged with the Department of Agriculture for the study of the possible relationship between potato blight and a congenital condition in which the spinal column of newborns is malformed. There are indications that a to. c compound in the diseased potato may be responsible for this congenital effect.

There is a great need for research-trained individuals in clinical pharmacology and toxicology. It is estimated that currently only 25-30 individuals are actively investigating mechanisms of drug action in humans to develop safer and more effective therapy. In particular, studies of drug action in children and the genetic variability of drug action are areas which are short of well-trained scientists.

Program Plans in F.Y. 1975

The Pharmacology-Toxicology Program is a comprehensive program, including clinical pharmacology, toxicology, and biorelated chemistry. It supports research and research training through a variety of mechanisms. Research centers take advantage of and stimulate collaboration between scientists working on related research problems and also facilitate the involvement of clinical scientists. Research supported by this program is providing a rational basis for the safer use of presently available drugs and is contributing to the design of more effective therapeutic agents.

The biorelated chemistry portion of the program provides the chemical understanding of both living systems and inanimate molecules requisite for design and synthesis of chemical therapeutic agents having specific limited effects with a minimum of undesired side actions. It includes, inter alia, work on naturally occurring potential medicinal materials from plants and animals as well as highly sophisticated methodology for structure determination and for synthesis of active molecules.

Among examples of research accomplishments may be mentioned the study, at one of the centers, of a new class of anti-hypertensive agents which act by peripheral vasodilatation. One of these, minoxidil, appears to be an extremely promising compound relatively free from side effects and yielding relatively prompt responses after administration.

The Program has given a great deal of attention to the area of drug metabolism. A drug rarely remains unchanged in the body; the vast majority are transformed to other chemicals which are, in some cases, inactive, but in other cases, more active than the original drug. In some instances, the transformed drug is highly toxic; examples are the epoxide metabolites formed in the liver. A great deal has been learned about drug interactions. A good example is the effect of the anti-depressant drug, imipramine, on the effectiveness of the anti-hypertensive agent, guanethidine. In the presence of imipramine, guanethidine has almost no effect on hypertension. Work on mercury poisoning at the center at the University of Rochester has brought out an improved method for detoxifying a victim. The organic compound, methyl mercury, is removed by the addition of the amino acid, cysteine, to the blood stream, as it is shunted into an extracorporeal dialysis machine, which removes both the methyl mercury and the cysteine from the blood, which is then returned to the circulation.

Biomedical Engineering

Authorizing Legislation: Public Health Service Act, Title IV, Part E

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits.....	---	---	---	---	---	---
Other expenses.....		$20,428,000		$18,249,000		-$2,179,000
Total.....		20,428,000		18,249,000		-2,179,000
Budget Mechanism:						
Research Grants:						
Regular program:						
Noncompeting.....	57	6,428,000	94	8,729,000	+37	+2,301,000
Competing.....	64	4,142,000	12	882,000	-52	-3,260,000
Subtotal Regular	121	10,570,000	106	9,611,000	-15	-959,000
Special programs:						
Diagnostic Radiology Research Centers.....	2	972,000	2	1,000,000	-0-	+28,000
Biomedical Engineering Research Centers.....	6	2,079,000	6	2,200,000	-0-	+121,000
Research Career..	17	426,000	15	321,000	-2	-105,000
Scientific Evaluation.....	---	68,000	---	136,000	-0-	+68,000
Subtotal Special	25	3,545,000	23	3,657,000	-2	+112,000
Fellowships 1/.....	56	1,252,000	7	267,000	-49	-985,000
Training Grants 1/.	430	3,783,000	430	3,783,000	-0-	-0-
Research & Development Contracts...	4	1,278,000	2	931,000	-2	-347,000
Total.....		20,428,000		18,249,000		-2,179,000

1/ Numbers reflect full time equivalent

Program Plans in F.Y. 1976

In response to Congressional and Advisory Council recommendations, the Biomedical Engineering Program continues to support a grant program of biomedical engineering research centers to exploit further the growing relationship between engineering, biology, and medicine. The efforts of these centers will be variously balanced between research, development, and application, and they are expected to serve as regional foci for special-purpose research or development. Emphasis in the regular research program will be on (1) research on the use of the principles and practices of engineering science to explore life processes at the molecular level; (2) the application of engineering control theories to the study of physiological processes; (3) microelectronic instrumentation for biophysical studies of patients; and (4) the use of radiosotopes and ultrasound, infrared, and laser radiation for the improvement of diagnostic radiology.

A whole segment of the program is devoted to the automation of the clinical laboratory, in order to (1) improve the current methods used in the clinical laboratory; (2) develop new methods; (3) develop new strategies for reaching a diagnosis with the help of the laboratory; and (4) develop automated technology not only for the clinical chemistry laboratory, but also for the hematology and microbiology areas. There is currently a shortage of individuals who combine a strong background in biomedical research with an interest in applying the results to rapid and accurate laboratory diagnosis. The postdoctoral research fellowship program in clinical laboratory science seeks to respond to this need.

Program Plans in F.Y. 1975

The main objectives of the Biomedical Engineering Program are to support the effective introduction of the principles and practices of engineering science into fundamental and applied biomedical research, and to support quality research training in the area. In selected instances, prototype instrumentation and devices are developed that will be useful in improvement of health care.

Research support is provided for theoretical, developmental, and applied aspects of biomedical instrumentation, biomaterials, computers in biomedical research, and application of physical science and engineering principles in health care. An example of this type of research is the development of an instrument by investigators at Berkeley, California, which is capable of finding, measuring, counting, and carrying out elaborate pattern recognition operations on bacterial colonies as they grow on nutrient media in the laboratory. This also allows recognition of bacterial mutants which have been of immense utility in molecular biology. The automation of the detection and isolation of such mutants will speed up such laboratory work manyfold. Currently, over 100,000 bacterial colonies can be examined automatically by this instrument per week.

In the section on automation of the clinical laboratory, work is concentrated on making clinical laboratory tests and procedures more reliable, accurate, rapid, and cheaper; and to this end new and more efficient biochemical methods, improved instrumentation, and appropriately automated technology is being developed. Emphasis will be given to research and development on (1) advanced analytical instrumentation systems, (2) the establishment of normal values for clinically important measurements, (3) the automated diagnosis of viral disease, and (4) patient sample identification systems. In recent years, the Institute has supported the development of a remarkable new instrument for performing blood chemical analyses in the clinical laboratory. Using principles of centrifugation, investigators at the Oak Ridge National Laboratory have carried out analyses more rapidly and at reduced unit cost. In the past year, a miniaturized, more manipulable version has been developed which uses micro quantities of samples and reagents, and this is now being adapted for use in the blood bank.

Clinical and Physiological Sciences

Authorizing Legislation: Public Health Service Act, Title IV, Part E

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits.....	---	---	---	---	---	---
Other expenses.....		$21,008,000		$19,393,000		-$1,615,000
Total.....		21,008,000		19,393,000		-1,615,000
Budget Mechanism:						
Research Grants:						
Regular program:						
Noncompeting.....	36	2,376,000	31	2,209,000	-5	-167,000
Competing.....	16	1,187,000	5	247,000	-11	-940,000
Subtotal Regular	52	3,563,000	36	2,456,000	-16	-1,107,000
Special programs:						
Anesthesiology Research Centers.	5	3,028,000	6	3,190,000	+1	+162,000
Trauma and Burn Research Centers.	16	5,200,000	15	5,200,000	-1	-0-
Research Career....	12	328,000	9	245,000	-3	-83,000
Scientific Evaluation.....	---	19,000	---	19,000	-0-	-0-
Subtotal Special	33	8,575,000	30	8,654,000	-3	+79,000
Fellowships 1/.....	70	750,000	14	163,000	-56	-587,000
Training Grants 1/.....	921	8,120,000	921	8,120,000	-0-	-0-
Total.....		21,008,000		19,393,000		-1,615,000

1/ Numbers reflect full time equivalent

Program Plans in F.Y. 1976

The ongoing program of research grants, anesthesiology and trauma and burn research centers, research training grants, and fellowships will be pursued vigorously, with increases or special emphasis in the areas of trauma and burn research and the control of pain. The program encompasses the areas of anesthesiology, trauma and burn research, and the behavioral sciences. Additional support for the trauma and burn research program of NIGMS would permit the opportunity for new research centers and projects to explore new approaches to the complex biomedical problems associated with trauma and burn injuries. The field of trauma and burn research is still new enough to offer many fertile areas of investigation. At a workshop sponsored by the NIGMS in May 1974 the areas of wound healing, control of infection, and the proper treatment of burn injuries were noted to need more emphasis. The Institute expects to actively program applications of high quality in these areas and to expand its ongoing in-depth studies in other vital areas.

Within the area of anesthesiology, the control of pain is becoming a new focus. It has many different aspects, several of which fall within the Clinical and Physiological Sciences Program: (1) the pharmacologic aspect, concentrating on the chemical means of controlling pain; (2) the behavioral aspects, studying the problem analytically to establish a basis for rational treatment; and (3) an analysis of the mechanism of action of acupuncture. There is no question about the central importance of pain control, but the scientific leads toward an understanding are few in number. Nonetheless, increasing opportunities appear to be developing.

The Program's behavioral sciences section is growing slowly as behavioral scientists begin to investigate subjects of mutual interest to health scientists. An area of theoretical, and possibly soon of more practical importance is behavioral genetics, which, put another way, deals with animal and human behavior as phenotypic expressions or characteristics which can be studied and analyzed with genetic techniques.

Program Plans in F.Y. 1975

Traumatic and burn injuries are the leading causes of death between the ages of 1 and 44 and the fourth leading cause of death in all age groups. Events leading to death from such injuries are frequently associated with sequential failure of organ systems. Survival depends greatly on the early recognition and reversal of these effects. Therefore, a broad range of research on the changes in the cardiovascular, pulmonary, renal, endocrine, and nervous systems is necessary to discover better ways to prevent death, mitigate pain, and lessen the degree of disability caused by the injuries.

The Program includes individual projects on fluid therapy in shock, metabolic changes in the traumatized patient, organ failures, wound healing, pathophysiology of burns, septic shock, and computer assessment of the extent of injury. A large project relating to circulatory and fluid volume changes in burns was started this year at a new research center located in Boston, where studies will be devoted to the metabolic changes, pulmonary complications, and wound healing following severe burns. Investigators at other centers are involved in studies of energy exchange, cellular and subcellular changes in shock, infection, pulmonary physiology, and patient monitoring of the critically ill.

The specific objectives of the anesthesiology segment are to support basic and clinical research in anesthesia as a basis for improved care of patients requiring surgical procedures, respiratory assistance, or relief from chronic pain. The program includes research on the use of anesthestic agents, basic physiologic and metabolic changes caused by anesthetics, management of respiratory failure,

resuscitation, and intensive care. The NIGMS continues to support research on acupuncture. In the current year we are supporting six projects dealing with the basic mechanism of action of acupuncture and its relative effectiveness compared to other therapy for pain.

There is a growing acceptance of the role of behavioral scientists in the research, teaching, and practice of medicine. Research done in a medical setting by behavioral scientists is more likely to have an impact on health than if done in isolation. Support of postdoctoral research training focused on trauma problems, anesthesiology, and behavioral science is viewed as an essential element in securing good future research applications in these very important areas. In each instance, the program seeks to identify training situations where both basic and clinical training and research can come together.

Genetics

Authorizing Legislation: Public Health Service Act, Title IV, Part E

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits.....	---	---	---	---	---	---
Other expenses.....		$51,205,000		$42,483,000		-$8,722,000
Total.....		51,205,000		42,483,000		-8,722,000
Budget Mechanism:						
Research Grants:						
Regular program:						
Noncompeting.....	329	23,908,000	417	27,131,000	+88	+3,223,000
Competing.....	232	10,074,000	44	2,447,000	-188	-7,627,000
Subtotal Regular	561	33,982,000	461	29,578,000	-100	-4,404,000
Special programs:						
Genetic Research Centers.....	9	6,681,000	10	6,500,000	+1	-181,000
Research Career...	102	2,489,000	73	1,872,000	-29	-617,000
Scientific Evaluation.....	---	101,000	---	101,000	-0-	-0-
Subtotal Special	111	9,271,000	83	8,473,000	-28	-798,000
Fellowships 1/.....	238	4,913,000	98	1,680,000	-140	-3,233,000
Training Grants 1/..	297	2,600,000	297	2,600,000	-0-	-0-
Research & Development Contracts....	3	439,000	3	152,000	-0-	-287,000
Total.....		51,205,000		42,483,000		-8,722,000

1/ Numbers reflect full time equivalent.

Program Plans in F.Y. 1976

The ongoing program of research grants, genetics centers, training grants, fellowships, and research and development contracts will be pursued vigorously, with increases or special emphasis in the following areas; uncovering of the basic lesions responsible for genetic disease; preventive technology; tissue culture studies of mammalian systems; and techniques for early identification of individuals destined to suffer late-onset genetic illness, such as Huntington's disease. The program will explore how genetic registries can best be utilized and what ethical issues are raised in the use of information from these registries. Currently, registries exist in many different formats, collected under many different auspices, and for many different purposes. More widespread availability could help to advance the study of human genetics.

The total pool of medical geneticists is about 300-strong, which is thought to be far short of the growing need. Each year, additional medical centers throughout the country open up medical genetics clinics and services and the staffing need is indeed great. The Institute plans to continue to support postdoctoral fellowships for individuals who combine backgrounds in basic genetics and medicine.

An area of crucial importance is the search for and study of chromosome markers. It is a striking fact that the transplantation from live donors of organs such as kidneys have, in the main, only succeeded when the donors were close relatives. This is so because the genetic system governing histocompatibility among unrelated individuals is at present not understood. In order to make such facilities as kidney banks generally useful, the capability of matching potential organ donors to the patients must be expanded.

Program Plans in F.Y. 1975

Genetics, more than most sciences and medical disciplines, must cut across fields. Basic scientific contributions to genetics come from chemistry, statistics, psychology, molecular and cell biology. Almost any area of medicine, be it anesthesiology or cardiology, has genetic aspects. Most serious and prevalent human diseases include genetic components.

The major part of the genetics program continues to focus on topics not directly related to disease entities. Research on nucleic acid chemistry and metabolism and on gene function are examples. Research using lower organisms--bacteria, fungi, fruit flies--continues to be extensively supported. In this respect, the program is considered a long-range resource, generating concepts applicable to all of genetic disease.

In the past few years, increased emphasis has been given to proposals by molecular biologists interested in the genetics of mammalian systems, including man. This trend, which we consider desirable and welcome, can be attributed to several recent developments: (a) improvements in technology, particularly in tissue culture and somatic cell genetics, and (b) an increased interest in and capability of the molecular biologists to extend the conceptual framework of gene action, now largely based on work with lower organisms, to the more complex eukaryote systems.

Within the field of human genetics, the NIGMS supports research that promises to yield new concepts and generalizable new modes of therapy. For this purpose, diseases such as Lesch-Nyhan disease and glucose-6-phosphate dehydrogenase deficiency become objects of study. These are illnesses that might not be of interest to categorical Institutes, since the former is extremely rare but serious, while the latter is fairly common but ordinarily quite benign. The study of these two conditions has been disproportionately fruitful in delineating aspects of

human somatic mutation, chromosome mechanics, human developmental genetics, and the interaction of drug therapy and genetic predisposition.

The 10 genetic centers, two of which were initiated in F.Y. 1974, combine basic research with clinical application and provide excellent settings for the clinical evaluation of new findings through their involvement in genetic community services, such as counseling. For example, researchers at the genetic center at Yale University are trying intensively to map the human chromosomes. This work has great practical potential in helping to find ways to detect diseases, such as Huntington's disease, early in life. Huntington's disease usually does not manifest itself until the ages of 20 or 30, and there are no known biochemical changes detectable before that time. One way of detecting carriers of this disease would be to discover closely linked markers, which is one of the objectives of the mapping studies.

Cellular and Molecular Basis of Disease

Authorizing Legislation: Public Health Service Act, Title IV, Part E

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses		$60,766,000		$48,687,000		-$12,079,000
Total		60,766,000		48,687,000		-12,079,000
Budget Mechanism:						
Research Grants:						
Regular program:						
Noncompeting	349	23,862,000	426	23,909,000	+77	+47,000
Competing	237	9,627,000	39	1,968,000	-198	-7,659,000
Subtotal Regular	586	33,489,000	465	25,877,000	-121	-7,612,000
Special programs:						
Molecular Pathology Research Centers	1	500,000	2	1,200,000	+1	+700,000
Research Career	91	2,232,000	70	1,674,000	-21	-558,000
Scientific Evaluation	---	116,000	---	150,000	-0-	+34,000
Subtotal Special	92	2,848,000	72	3,024,000	-20	+176,000
Fellowships 1/	259	6,375,000	77	2,082,000	-182	-4,293,000
Training Grants 1/	2,053	18,054,000	2,053	17,704,000	-0-	-350,000
Total		60,766,000		48,687,000		-12,079,000

1/ Numbers reflect full time equivalent.

Program Plans for F.Y. 1976

While continuing to support fundamental research within the basic biomedical disciplines that have contributed so strongly to the cell sciences over the past score of years, the Cellular and Molecular Basis of Disease Program is increasing its emphasis on multidisciplinary approaches to the complex problems of the structure and function of the wide variety of cells, their membranes, and subcellular organelles, that make up the organs and tissues of the human body. Particular attention will be given to the continued development of molecular pathology centers of high quality.

Because bright, eager young minds are the lifeblood of a highly creative research enterprise, emphasis in the training of young scientists during the coming year will be aimed at multidisciplinary programs that give students access to a broad array of research opportunities, talent and experience within a given institution, as they prepare for their future careers in the cell sciences. Special attention will be given to training programs that interrelate the basic sciences and pathology so as to give pathologists, whose primary interest is the study of disease, greater insight into the knowledge, capabilities, and techniques of the basic science disciplines, while at the same time bringing to the basic sciences many of the challenges and opportunities for fundamental research that are found in the study of the diseased state.

Program Plans in F.Y. 1975

The Cellular and Molecular Basis of Disease Program deals at the fundamental science level with the structure and function of the cellular machinery common to all living organisms. Almost nothing was known about the cell's internal machinery when the NIH extramural programs were initiated in 1946. The support of creative scientists and the availability of microscopes, ultracentrifuges, spectrophotometers, and other sensitive instruments, made available largely through Federal funds, have led to the discovery, description, and study of the tiny organs, or "organelles," that are a part of all cells. These organelles have vital roles in all life processes. The mitochondria, for instance, are now known to be the "power plants" of the cell and to have a role fully as significant to the life of each cell as the heart to the human body. Among scientists doing research on mitochondria, one key group is keenly interested in exploring the manner in which these organelles are formed within cells. It has been found that mitochondria contain their own DNA. Scientists supported by this program have found that the hereditary information for certain key proteins of the mitochondria are coded for by this DNA and are synthesized independent of the DNA of the cell nucleus.

Knowledge of these cellular organelles and how they become deranged in disease is the basis for the newly emerging field of "molecular pathology," which brings the evolving knowledge of biochemistry, biophysics, and other basic medical disciplines to bear on the molecular alterations of cells and their organelles.

The past year has seen the establishment of the first Center in Molecular Pathology, at Yale University, for research on cellular membranes, under the leadership of Dr. George Palade, who was awarded the Nobel Prize for his pioneering research on the internal structure of the cell and its organelles.

The fundamental research being conducted by scientists in the CMBD program is providing the creative stimulus to important new discoveries throughout the biomedical research enterprise. NIGMS-supported investigators have shown that colchicine, a drug commonly used as therapy for gout, binds to long, rod-shaped organelles called microtubules that are present in all cells. The microtubules play many roles. For instance, they are responsible for lining up the chromosomes

properly during cell division. They are the basic mobile components of cilia, which line the respiratory passages; and of flagella, which form the tails of sperm cells. Microtubules are important structural components in nerves and are thought to have an important role in the movement of neural transmitters along the nerve fibers to the nerve endings. Understanding of the formation, structure, and function of microtubules has broad implications for our understanding of many diseases, ranging from cancer to mental illness, and the knowledge being gained by basic scientists is avidly sought by investigators working in the wide range of clinical specialties.

The above examples show how new, basic information developed in the exciting and rapidly moving fields of the cellular and molecular sciences becomes important to clinically oriented programs supported by the categorical Institutes.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Title IV, Part E

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	155	$2,840,000	152	$3,098,000	-3	+$258,000
Other expenses.....	---	3,287,000	---	4,149,000	---	+862,000
Total.....	155	6,127,000	152	7,247,000	-3	+1,120,000
Budget Mechanism:						
Research Management and Program Services.	155	6,127,000	152	7,247,000	-3	+1,120,000
Total.....	155	6,127,000	152	7,247,000	-3	+1,120,000

This program provides for the overall leadership and staffing necessary for the administration and management of the research effort of the Institute and supports the National Advisory General Medical Sciences Council. In 1976, the professional and supporting staff will continue to maintain close surveillance and guidance required for the many programs of the Institute.

The net increase of $1,120,000 reflects a built-in decrease of $132,000 in the payment to the NIH Management Fund for centrally furnished services offset by a built-in increase of $1,252,000 which provides: $32,000 for within-grade pay increases; $13,000 for an extra day of pay in 1976; $12,000 for increased cost of using the Federal Telecommunications System; $2,000 for postage increase; $195,000 for the Research Management and Program Services portion of the October 1974 pay raise annualization cost; $613,000 for increased costs in General Expense and Program Evaluation; and $385,000 for increased operating costs.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Pharmacology-Toxicology (Public Health Service Act, Title IV, Part E)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$27,756,000	Indefinite	---	$25,571,000

Purpose: The purpose of the pharmacology-toxicology program is to improve medical therapy through acquisition of increased knowledge of the mechanisms of drug action, of ways to increase efficacy and safety, and to diminish toxicity.

Explanation: This program supports research through regular research grants, special center grants, fellowships, training grants, and contracts. This program also funds direct training for 18 intramural NIH "research associates."

Accomplishments, 1974/1975: A total of 369 research grants, centers, fellowships, and training grants and three contracts were funded in 1974. Research in enzymatic metabolism, body distribution, and excretion of drugs will be pursued on a broad front. Applications of sophisticated new analytical techniques, such as gas chromatography - mass spectrometry, use of compounds labeled with stable isotopes, and radio-immuno assay, will accelerate progress in these areas. Computer technology and the skills of synthetic bio-organic chemists will be applied to efforts to develop improved therapeutic agents.

Objectives, 1976: Unifying principles established through basic research will be further applied to problems in therapy. Emphasis will be devoted to emerging opportunities, especially in pharmacogenetics, immunopharmacology, pharmacokinetics, and dermatopharmacology. A continuing effort will be made to assess the risks from adverse drug reaction and from drug-drug interactions, as well as to determine the efficacy of commonly utilized drugs. Additional emphasis will be given to the activities encompassed within the pharmacology-toxicology research centers.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Biomedical Engineering (Public Health Service Act, Title IV, Part E)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$20,428,000	Indefinite	---	$18,249,000

Purpose: The purpose of the biomedical engineering program is to support the effective introduction of engineering science into fundamental and applied biomedical research. Prototype instrumentation and devices are being developed that will be useful in the improvement of health care.

Explanation: This program supports research through regular research grants and special center grants. Contracts are utilized for the support of applied research and development. A number of individuals in clinical chemistry, biomedical engineering, and diagnostic radiology have been and are currently being supported through fellowships and training grants.

Accomplishments, 1974/1975: This program was supported by a total of 208 research grants, centers, fellowships, training grants, and five contracts in 1974. Research accomplishments included the development of systems for rapid data acquisition and display, involving new types of transducers and integrated electronic circuitry, instrumentation for positive patient/sample identification, automated laboratory procedures and new techniques in diagnostic radiology.

Objectives, 1976: Improved systems for the automation of clinical laboratories will be developed. One or two new biomedical engineering research centers will be established in 1976. These centers will provide a focal point where interdisciplinary interaction can take place between physicians, scientists, and engineers. Emphasis will be placed on the application of engineering control theory to the study of physiological processes, computer-aided clinical decision making, instrumentation research and development, and the use of integrated electronics in medicine. These centers will require the development of prototype university patterns and new institutional forms that are appropriate for advancing the interaction between engineering and biomedicine.

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NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Clinical and Physiological Sciences (Public Health Service Act, Title IV, Part E)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$21,008,000	Indefinite	---	$19,393,000

Purpose: The purpose of the clinical and physiological sciences program is to promote and foster basic and clinical research in the physiological sciences and in certain clinical areas, particularly anesthesiology and trauma.

Explanation: This program supports research through regular research grants, special center grants, as well as fellowships and training grants.

Accomplishments, 1974/1975: This program was supported by a total of 198 research grants, centers, fellowships, and training grants in 1974. The Institute has begun to explore its role in the support of research on acupuncture in surgical anesthesia and in relief of chronic pain. The increasing involvement of anesthesiologists in the total respiratory care of patients is the stimulus for developing improved methodologies and devices for diagnosis and treatment of hypoxia, complications from anesthesia, and cerebral vascular insufficiencies. The effectiveness of acupuncture in surgical anesthesia and in relief of chronic pain will be further explored. Many aspects of wound healing, mechanisms of shock, and other factors related to trauma will be supported.

Objectives, 1976: A number of research opportunities have been identified by Institute staff and consultants in recent workshop conferences. Research will be extended into these basic physiologic and applied clinical areas--including studies of pain and its control, bone and wound healing, control of infection and the proper treatment of burn injuries.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Genetics (Public Health Service Act, Title IV, Part E)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$51,205,000	Indefinite	---	$42,483,000

Purpose: The purpose of the genetics program is to support research aimed at the prevention, therapy, and control of genetic diseases in man, including those multifactorial illnesses with a strong hereditary component.

Explanation: Genetic research is supported through regular research grants, centers, training grants, fellowships, and contracts. The NIGMS approaches the problem of human genetic disease as a generalized phenomenon involving common mechanisms, and amenable to elucidation on the basis of a broad fundamental research approach.

Accomplishments, 1974/1975: The genetics program was supported in 1974 by a total of 747 research grants, centers, fellowships, training grants, and three contracts. Particular attention will be devoted to genetic mapping of the human chromosome, identification of carriers of genetic disease, and control mechanisms for genetic expression in man. The contract-supported "Human Genetic Mutant Cell Repository" will provide seed stocks of well-characterized human tissue culture cells to researchers in the field.

Objectives, 1976: Attention will be given to monitoring some of the newer approaches to treatment of genetic disease, with encouragement of support for methodologies which appear scientifically sound and justified. Special emphasis will be given to: uncovering of the basic lesions responsible for genetic disease, preventive technology, tissue culture studies of mammalian systems, and techniques for early identification of individuals destined to suffer late-onset genetic illness, such as Huntington's disease.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Cellular and Molecular Basis of Disease (Public Health Service Act, Title IV, Part E)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$60,766,000	Indefinite	---	$48,687,000

Purpose: The purpose of the cellular and molecular basis of disease program is to support research on the structure and function of human cells and their component parts, with the expectation that a greater understanding of these aspects will contribute to ultimate control of all forms and manifestations of disease.

Explanation: This program supports research through regular research grants, centers, fellowships, and training grants.

Accomplishments, 1974/1975: This program was supported by a total of 932 research grants, fellowships, and training grants in 1974 and one contract. Research support in the fields of anatomical sciences, biochemistry, biophysics, microbiology, and pathology will contribute to the goals of this program. Research encompasses detailed studies of the structure of cellular organelles, their function under normal and diseased conditions, and responses to injury and aging. Enormous advances have been made recently in our understanding of the chemical structure of cell membranes, their microscopic appearance, and their manifold functions, including the highly selective transport of material in solution from outside the cell, and vice versa. The base of knowledge in cell biology will be broadened by molecular studies of proteins, metabolic reactions, and cell transport. The first center in Molecular Pathology has been established at Yale University.

Objectives, 1976: Research in cell differentiation and specialization will be emphasized. Newer instruments for investigating cell structure, such as the high voltage scanning electron microscope, will be exploited for the study of membranes and other subcellular components.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Research Management and Program Services (Public Health Service Act, Title IV, Part E)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
155	$6,127,000	Indefinite	152	$7,247,000

Purpose: This program provides for the overall leadership and staffing necessary for the administration and management of the research effort of the Institute and supports the National Advisory General Medical Sciences Council.

Explanation: The National Institute of General Medical Sciences supports a broad base of fundamental and applied biomedical research programs aimed at the solution of certain major health problems. The Institute Director and her staff are responsible for the overall direction, planning, and evaluation of these programs.

Accomplishments, 1974/1975: The Director and supporting professional and clerical staff provided continuing guidance and surveillance over the pharmacology-toxicology, engineering in biology and medicine, clinical and physiological sciences, genetics, and cellular and molecular basis of disease programs of the Institute. A total of 2,454 research grants, special center grants, fellowships, training grants, and 12 research contracts were funded in 1974. It is estimated that approximately 2,884 grants and fellowships and 12 research contracts will be funded in 1975.

Objectives, 1976: In 1976, the professional and support staff will continue to maintain close surveillance and guidance required for the many programs of the Institute.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$161,630,000	$40,295,000
Total obligations	161,630,000	40,295,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Pharmacology-Toxicology	---	$25,571,000	---	$6,032,000
Biomedical Engineering	---	18,249,000	---	4,705,000
Clinical and Physiological Sciences	---	19,393,000	---	4,525,000
Genetics	---	42,483,000	---	12,497,000
Cellular and Molecular Basis of Disease	---	48,687,000	---	10,919,000
Research Management and Program Services	152	7,247,000	152	1,617,000
Total obligations	152	161,630,000	152	40,295,000

Obligations by Object

	1976 Estimate	Interim Budget
Total number of permanent positions	152	152
Full-time equivalent of all other positions	5	5
Average number of all employees	154	154
Personnel compensation:		
Permanent positions	$2,697,000	$701,000
Positions other than permanent	110,000	34,000
Other personnel compensation	99,000	16,000
Subtotal, personnel compensation	2,906,000	751,000
Personnel benefits	562,000	97,000
Travel and transportation of persons	100,000	20,000
Transportation of things	34,000	9,000
Rent, communications, and utilities	309,000	77,000
Printing and reproduction	175,000	35,000
Other services:		
Project contracts	3,000,000	1,219,000
Payment to NIH Management Fund	1,773,000	443,000
Other	1,704,000	254,000
Supplies and materials	79,000	18,000
Equipment	53,000	14,000
Grants, subsidies, and contributions	150,935,000	37,358,000
Total obligations by object	161,630,000	40,295,000

Justification

National Institute of General Medical Sciences

Interim Budget

The estimate for the three-month interim period reflects a continuation of the programs of the National Institute of General Medical Sciences consistent with the 1976 Estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

THURSDAY, APRIL 17, 1975.

WITNESSES

DR. NORMAN KRETCHMER, DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. PHILIP A. CORFMAN, DIRECTOR, CENTER FOR POPULATION RESEARCH, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
JOEL R. HEDETNIEMI, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
H. RICHARD MILLER, FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD J. FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We have the National Institute of Child Health and Human Development.

This presentation will be made by Dr. Norman Kretchmer, Director. We have a biographical sketch of you, Doctor, which we will place in the record at this point.

Name: Norman Kretchmer, M.D., Ph. D.

Position: Director, National Institute of Child Health and Human Development.

Birthplace and date: New York, N.Y., January 20, 1923.

Education: Cornell University, 1944, bachelor of science; University of Minnesota, 1945, master of science; University of Minnesota, 1947, doctor of philosophy; State University of New York, College of Medicine, 1952, doctor of medicine.

Experience: Present—Director, NICHD; Acting Director, NIA; clinical professor of pediatrics, Howard University; consultant/lecturer, National Naval Medical Center, Bethesda, Md.; 1970—Visiting professor, University of Lagos, Lagos, Nigeria; 1969–74—Chief, Section of Developmental Medicine, Stanford University; professor of pediatrics, Stanford University; 1969–72—Chairman, Program in Human Biology, Stanford University; 1959–69—Professor and executive head, pediatrics, Stanford University; 1958–59—Associate professor of pediatrics, Cornell University; 1956–58—Assistant professor of pediatrics, Cornell University; 1953–56—Assistant professor of biochemistry in pediatrics, Cornell University; 1950–55—Lecturer of biology, Brooklyn College; 1948–52—Fellow and research associate of pathology, Long Island College of Medicine; 1947–48—Assistant professor, pathology and biochemistry, University of Vermont; 1944–47—Teaching assistant, University of Minnesota.

Professional societies: American Academy of Pediatrics (fellow); American Association for Advancement of Science (fellow 1963); American Association for University Professors; American Board of Pediatrics (licentiate 1957); American Chemical Society; American Institute for Biological Sciences; American Pediatric Society; American Society for Biological Chemists; American Society for Clinical Nutrition; American Society for Clinical Investigation (council member 1964–67); American Society for Human Genetics; Association of American Medical Colleges; Chilean Pediatric Society (honorary); Chilean Society of Biology (honorary); Chilean Society of Endocrinology; Czechoslovakian Society of Pediatrics (honorary); Harvey Society; Histochemical

Society; International Organization for the Study of Human Development (president 1970–76); International Pediatric Association (standing committee member 1974–77); Italian Pediatric Society (honorary); Perinatal Research Society; Salt and Water Club; Sigma Xi; Societe Francaise de Pediatrie de Paris; Society for Growth and Development; Society for Pediatric Research (president 1967–68); Western Society for Clinical Research; Western Society for Pediatric Research (president 1966–67).

Publications: Numerous publications in the fields of developmental biochemistry, neonatology, genetics, and pediatrics.

Awards: 1973–74—Guggenheim Fellowship in Human Development; 1971—Harold K. Faber Professor of Pediatrics, Stanford University; 1969—Borden Award, American Academy of Pediatrics; 1969—Alumni Medallion for Distinguished Service to American Medicine, College of Medicine, Downstate Medical Center, New York; 1965–66—Commonwealth Fund Fellow, Atomic Energy Laboratory, Saclay, Paris; 1965—Honorary Member Faculty of Medicine, University of Chile; 1965—Alpha Omega Alpha (faculty); 1958—E. Mead Johnson Award for Research in Pediatrics, American Academy of Pediatrics; 1957—Commonwealth Fund Traveling Fellowship, St. Mary's Hospital, London and University of Paris; 1955–56 Henry L. Moses Alumni Prize in Basic Research, Montefiore Hospital; 1952–53—Commonwealth Fund Fellow, Montefiore Hospital.

Name: Philip A. Corfman, M.D.

Position: Director, Center for Population Research, National Institute of Child Health and Human Development.

Birthplace and date: Berea, Ohio; July 19, 1926.

Education: Oberlin College, 1950, Bachelor of Arts; Harvard Medical School, 1954, Doctor of Medicine.

Experience: Present—Director, Center for Population Research, NICHD; 1967–68—Chairman, Public Health Service Population Committee; 1967–68—Assistant to the Director for Population Research, NICHD; 1966–67—Acting Program Director, Reproduction Program, NICHD; 1965–66—Program Associate for Population Research, Reproduction Program, NICHD; 1964–66—Guest scientist, Navy Medical Research Institute, Bethesda, Md.; 1964–65—Consultant in Obstetrics and Gynecology, reproductive biology program, NICHD; 1963–64—Assistant visiting obstetrician and gynecologist, Harlem Hospital; 1963–64—Visiting fellow Vanderbilt Clinic, Columbia-Presbyterian Hospital; 1962–63—Member, Medical Executive Committee, Rip Van Winkle Foundation; 1960–63—Attending obstetrician, Columbia Memorial Hospital, Hudson, N.Y.; 1959–63—Obstetrician and Gynecologist, Rip Van Winkle Clinic, Hudson, N.Y.; 1956–59—Obstetrical and gynecological residency, Boston Lying-In Hospital and the Free Hospital for Women; 1956–59—Teaching fellow in obstetrics and gynecology, Harvard Medical School; 1954–56—Surgical internship and first year residency, Boston City Hospital, fifth surgical service (Harvard).

Professional societies: American Board of Obstetrics and Gynecology; American College of Obstetricians and Gynecologists; Food and Drug Administration Advisory Committee on Obstetrics and Gynecology; Population Association of America; Society for the Study of Fertility; World Health Organization Advisory Group to the Expanded Programme of Research, Development and Research Training in Human Reproduction.

Publications: Various publications on the development of contraceptives, cancer etiology, and cytogenetics.

Dr. KRETCHMER. Mr. Chairman, I would like to introduce the people with me. To my left are Mr. Joel R. Hedetniemi, Executive Officer; Dr. Philip A. Corfman, Director, Center for Population Research; and Mr. H. Richard Miller, the Financial Management Officer. Behind Dr. Corfman is Dr. Gilbert L. Woodside, our Acting Deputy Director.

Mr. FLOOD. You have a statement here, Doctor; how do you want to proceed with it?

Dr. KRETCHMER. If I may, I would like to read it, sir.

Mr. FLOOD. Proceed.

Dr. KRETCHMER. Mr. Chairman and members of the committee, I am pleased to have this opportunity to appear before you. Because

this is a new experience for me, I would like to discuss with you not only the accomplishments of the National Institute of Child Health and Human Development but also our goals and dreams, and how we intend to achieve our objectives. In the past, remarks by the Director of this Institute have included a summary of the research programs on aging.

Mr. FLOOD. How long have you been on board, Doctor?

Dr. KRETCHMER. Seven months, sir.

Following passage of the Research on Aging Act of 1974, however, these activities have been transferred to the National Institute on Aging, whose testimony I will present to you next. The separation of the aging program has given the National Institute of Child Health and Human Development an opportunity to examine its remaining programs, to reassess its mission, and to establish clearcut priorities.

MISSION

NICHD contributes to the good health and well being of the people of this Nation through study of the whole person rather than through study of a particular disease or organ of the body. We seek knowledge of how populations adapt to available resources; how people use methods of family planning; how the health of mothers, infants, and children can be assured; and how we can make major contributions to all of human development.

Our goal is to conduct and support research that will provide the knowledge needed to assure good health during pregnancy and infancy, as the foundation for development of the child and adolescent to full physical and mental adult potential. Interdependent with this goal is the need for better understanding of family structure, the dynamics of human populations, and population growth. I believe that this Institute can make the most important single contribution to general health, since the best form of adult health insurance is a healthy infancy and childhood. It is self-evident that many of the diseases that are encountered later in life have their beginnings in infancy and childhood, and in fact within the womb of the mother. This dependency of adult health on proper maternal and family environment is well accepted.

PROGRAM ORGANIZATION

Toward these ambitious goals of health for the Nation's adults, we have made significant shifts in the organization of the Institute. These changes were made to reflect our program focus on special areas of biomedical research as well as to improve administrative efficiency. Symmetrical with the Center for Population Research, a renowned unit for research in reproductive biology and studies of population growth and development, we have recently established a Center for Research for Mothers and Children. This new Center will support activities aimed at advancing knowledge on pregnancy, infancy, childhood, and early adult life. The Center also encompasses the subjects of sudden-infant-death syndrome and mental retardation, which require our special attention. The Center has responsibility for achieving a greater understanding of all health needs of mothers and children, from the earliest stages of pregnancy through the maturation of

the adult. We have taken particular care to ensure that both of our Centers coordinate their research efforts with other health agencies to move new knowledge quickly into programs for health care.

Through our two Centers, which work in conjunction with the outstanding investigators of our own intramural research program, we will be able to address special health problems by focusing on those areas which cause the most human suffering and the greatest economic loss. Our philosophy is "prevention" of maladies which affect all of mankind, since we deal mainly with the young and unborn.

Our emphasis is to prevent disease and disability in its early stages, so that long-range benefits will accrue to the adult. In an important sense, long-term disability may be more disastrous than infant mortality.

RESEARCH PRIORITIES

In the Center for Research for Mothers and Children, we have defined our approaches for attack on those areas which cause the greatest personal suffering and social cost. Areas of concentration will be on: the low birth-weight infant, the baby who is born too early or too small—approximately 250,000 infants in this Nation each year, of whom approximately 45,000 die and an equal number have disability; congenital malformations, including the effect of environment upon the unborn and newly born child; the high-risk pregnancy, which affects primarily the poor and the young; labor and the birth process, especially concerning basic information about how a woman begins labor; communicative disorders, learning disabilities, and nutrition problems of children; and finally, those diseases of infancy and disabilities in human development which would be encountered in studies of the sudden-infant-death syndrome and the precursors to mental retardation.

The Center for Population Research continues its leadership role in study of the causes and effects of population growth and change, development of contraceptive methods and their evaluation, and fundamental research in reproductive biology. In the Center's continuing program, special attention will be given to: clinical trials of contraceptive agents for men; safety of intrauterine devices and oral contraceptives; economic, sociologic, and environmental consequences of population change; teenage pregnancies; and motivation for family planning.

Closely related to the extramural research activities of population and mother and child will be the Institute's new Perinatal Biology Center at NIH. This facility, which allows us to marshal an array of professional talent and resources, will house innovative studies of pregnant women, newborn infants, and children regarding disorders associated with high-risk pregnancy and diseases which affect newborns. Further, through this Center we can provide a model of the kinds of interdisciplinary research which can be stimulated in similar kinds of centers throughout the Nation.

RESEARCH ADVANCES

We have seen a number of research advances over the past year, in our own laboratories and elsewhere.

In the area of reproductive biology, where we study both male and female reproductive processes, we have learned that sperm production is controlled by two hormones. The studies on binding of hormones, pituitary secretions, and related factors are most important in the search for effective male contraceptives. Another major research achievement by this Institute has been the identification of hormones released by a part of the brain called the hypothalamus, which controls the release of other hormones responsible for ovulation. One of these hormones has now been made in the laboratory and is being used and distributed throughout the world by NIH as a research agent for a variety of disorders in reproduction. But one of the big issues is to regulate the production of eggs in the female, and we support several laboratories synthesizing chemicals which can reduce the hormone responsible for ovulation and thus block the release of ova. At the same time, because we have been particularly concerned about the relationship of contraceptives and congenital malformation, we are developing projects to explore indications that use of oral contraceptives during the early part of pregnancy is associated with malformations of the heart and limbs.

Among the many social and behavioral aspects of population science, investigators have indicated that early social experience regarding roles for men and women has an important influence upon both family size and women's participation in the labor force. Another long-term study is providing information about women's motivation for family planning, their own roles, and their decisions on childbearing and spacing, family problems, and a variety of other issues related to the quantity and quality of succeeding generations.

The field of research on special health problems of mothers and children has produced notable results, too. Particularly of interest are the continuing developments regarding the sudden-infant-death syndrome, or crib death, an area where we are expending about $5.2 million. Contrary to earlier belief, new research indicates that babies who succumb to SIDS may not be totally healthy, but that they have been subjected to stress for some time before the occurrence of SIDS.

An Institute-supported investigator has found that SIDS babies have had an overgrowth and thickening of muscles surrounding the small pulmonary arteries, indicating a previous lack of oxygen in the system for varying periods of time. This pathology is known to occur in adults as well as infants. Our goal here is simply to prevent these tragic, unexpected deaths and, by virtue of prevention, avoid the loss of 7,500 children in this Nation each year. Meanwhile, we must gain some understanding of the mechanism involved in the problem.

A second area of concern, mental retardation, is a problem which afflicts all sectors of the population and causes anguish to families and society for decades. Major causes of mental retardation are events which can be sustained during the time the child is in the womb as well as the traumatic events suffered during labor and delivery.

From its inception, the Institute has had as one of its objectives the development of knowledge that would provide practicing obstetricians and pediatricians a variety of techniques for monitoring the condition of the unborn infant during labor and the birth process.

One approach is electronic monitoring, and recent research has led to the development of a prototype of a fetal risk index, a system for predicting the baby's health at delivery, and in the future. This research requires computer analysis, and will provide a continuous assessment of the fetal states, permitting timely intervention to prevent damage to the baby during labor.

Another new finding is that of a condition called the fetal-alcohol syndrome. Investigations have shown that babies of women with chronic alcoholism have impaired intellectual ability, small head, growth deficiency, and other serious problems.

Another finding is that zinc deficiency causes failure to thrive in infancy and a condition which makes a child eat unnatural foods, which is called pica. We have also supported research which is related to the determination of when a fetus is capable of surviving outside the mother, and a variety of chemical and physiological tests can be utilized now in a predictive fashion. Certain problems which originate with the mother or her baby contribute to the birth of a child who is too small and incapable of dealing with the outside world. One of these problems is sustained by infants of diabetic mothers; other situations are associated with infections, hypertension, or a variety of systemic diseases within the mother. There is no question that environmental factors, such as nutrition or the use of various therapeutic agents, such as drugs, will have an effect upon the well-being of the developing infant and the child he becomes.

NICHD CHALLENGE

Summarizing the work that is going on within this Institute, we should say that we are challenged to develop knowledge for family planning and the motivation for family planning; and that we are dedicated to insuring that each woman, when she gives birth, will have the most healthy baby that advanced medical science can guarantee, and that this infant will develop as an adult who has attained his greatest potential, free of diseases and disability.

I feel very deeply that, as our advances in knowledge increase, this information and new techniques must be made known to all members of society. Since I have recently come to the Institute from outside the Federal Government, I must say that it is important to me to see that the various members of our community, which include not only the research scientists but also the providers of health care and the lay public, receive information concerning our activities. I would like to mention that through the vehicle of journals read by practitioners, and in the development of material for parents and college and high school students, we are attempting to disseminate information regarding the development of man, and the kinds of special problems I have mentioned.

Mr. Chairman, I have found my few months here to be rewarding intellectually, since I believe that the greatest contribution that this biomedical and behavorial research Institute can make to the future of the Nation is through our mothers, children, and families. By attending and studying their special ills and problems today, we shall gain the best and most effective means of preventing these same afflictions tomorrow.

Mr. Chairman, the 1976 budget request for the National Institute of Child Health and Human Development is $106,062,000. I would be delighted to respond to any questions that you would like to ask of me and if necessary to supply whatever information you would require. Thank you for letting me have this opportunity to speak to you.

IMPACT OF REDUCTION

Mr. FLOOD. As you are new, I am pretty sure that Charlie Miller has briefed you on what the leadoff question usually is through these hearings, so I will bet you are waiting for me to ask it.

I will ask you: What is the impact on your program of the reduction in your budget of $20 million?

Dr. KRETCHMER. The impact of the reduction on our program is that we will be unable to fund about $20 million of noncompeting research grants.

Mr. FLOOD. Will you be able to meet all of your noncompeting grant commitments under this budget?

Dr. KRETCHMER. No, sir. We will be unable to fund approximately 327 grants for $19,484,000.

FETAL RESEARCH

Mr. FLOOD. Doctor, there was an article in Saturday's Washington Post concerning the Federal staff study recommending an end to the ban on fetal research. What effect did that ban on fetal research have on your research program?

Dr. KRETCHMER. In terms of our research program, the ban on fetal research had an effect on only two research projects. Most of the research we support was not affected by that ban because our research does not involve the living fetus.

Mr. FLOOD. Can you summarize for us the recommendations of that study group, just briefly now and then for the record if you feel you want to develop recommendations of the study group, develop the record for that.

Dr. KRETCHMER. I would be pleased to comment, but with certain reservations because the information that was reported in the Washington Post was premature. What was reported were the suggestions of the staff of the Commission rather than the Commission's recommendations. The Commission has now to react to the suggestions. The New York Times article on the same subject was more accurate. For me to summarize what the staff reported would be somewhat misleading. The Commission has to act on whatever the staff has offered.

Mr. FLOOD. What additional steps will have to be taken in order for these final guidelines to be published?

Dr. KRETCHMER. The Commission should make its report by the end of the month. The public will then have an opportunity to comment on the proposed regulations, after which the Secretary of the Department determines what the final regulations will be.

Mr. FLOOD. What kind of fetal research were you going to support in your 1976 budget?

Dr. KRETCHMER. We were not going to support any research on the living fetus, because we now operate under the current guidelines from the Department of Health, Education, and Welfare.

Mr. FLOOD. In your opening statement you say, "We have also supported research which is related to the determination of whether the fetus is capable of living outside the mother."

Would you elaborate on that research effort and tell us what you have learned out of that?

Dr. KRETCHMER. From the research, we have learned how to keep babies alive.

Mr. FLOOD. What have you learned?

Dr. KRETCHMER. A great deal. I can give you an example from my own background. Twenty years ago, when I was at Cornell we could not keep a baby alive who weighed below 1,000 grams, which is equivalent to about 2 pounds. All the babies below 1,000 grams died. Now, after the passage of 20 years, with new equipment, we are capable of keeping alive babies who weigh 600 grams and above at birth.

When I used the word "fetus" in the opening statement, I was talking about the fetus which is born as a premature infant. A major advance, then, has been to keep alive babies who start out in life at above 600 grams in contrast to above 1,000 grams as it was 20 years ago. Equally important is the work we are doing and the research we have accomplished to help assure that we are producing a healthier child and, hence, an adult with less disease and disability.

The data would indicate that we are decreasing the amount of disability in adults.

Mr. CONTE. Mr. Chairman, may I have a question on that?

Mr. FLOOD. Yes.

Mr. CONTE. In relation to the question the chairman asked you, you are dealing mostly with premature babies, as I understand it. But are you also looking into the question of abortion which is such a hot issue up here in the Congress and in the United States today?

Are you looking into the possibility of saving that child after its being aborted?

Dr. KRETCHMER. In a sense, Mr. Conte, the premature infant, the baby born at 37 or less weeks of gestation in contrast to the normal 40, is really a spontaneous abortion.

RESEARCH COORDINATION

Mr. FLOOD. In your opening remarks you say:

> We have taken particular care to insure that both of our centers coordinate their research efforts with other health agencies to move new knowledge quickly into programs for health care.

That is certainly very important.

Suppose you tell us who you are working with and give us a couple of examples of how you work with them.

Dr. KRETCHMER. We participate in two major committees within the Department. One, in the Office of the Secretary, is the DHEW Committee on Children, chaired by the Office of Child Development and on which NIH is represented by NICHD. At the level of the As-

sistant Secretary for Health, we have a Maternal and Child Health Policy Board which involves all the agencies from the Public Health Service. In our own Institute efforts, we have been discussing general programs and administration of programs with the Bureau of Community Health Services, specifically the Office for Maternal and Child Health, and with the Office of Child Development.

Relative to the behavioral sciences, we have been discussing program coordination with the National Institute of Mental Health.

Dr. Corfman, the Director of our Center for Population Research, chairs the Interagency Committee on Population Research which coordinates population research activities supported by Federal agencies and fosters the exchange of information among Federal population research programs. Also, Dr. Corfman's staff has close working relationships with the Food and Drug Administration, the World Health Organization, and a number of private agencies in the field of population and family planning.

ORAL CONTRACEPTIVES

Mr. FLOOD. Also in your justifications you state that you are going to investigate the possibility of improving the safety of the present oral contraceptives. What do you mean by improving the safety of oral contraception?

Dr. KRETCHMER. At the present, as has been reported in the newspapers, there are certain aspects of oral contraceptive agents that have risk. For example, some women respond by increase in blood pressure and hypertension.

Mr. FLOOD. What are the side effects of that?

Dr. KRETCHMER. One would be high blood pressure. Others would be the retention of water by the woman and pigmentation of the skin. By improving the chemical design, as we have seen proven with antibiotics, we hope to develop oral contraceptives which will not have these side effects.

Mr. FLOOD. How do you go about informing the practicing physician now that a particular group of these oral contraceptive users may have a higher risk for complications than another group.

Dr. KRETCHMER. I would like to ask Dr. Corfman to respond.

Dr. CORFMAN. A good example is the effects of pills on thromboembolism and stroke. We have established that if a woman takes the pills her chance of stroke is greater. A result of this finding has been to decrease the dosage of the drug. We have already shown from our data that the numbers of strokes have decreased.

This is a very practical example of how our research has resulted in benefits to the health of the country. We have informed the community through our own publications and particularly through dealings with FDA and the drug manufacturers.

Mr. FLOOD. That is what I wanted to know.

NUTRITION RESEARCH

Now, Doctor, suppose you describe for us your nutrition research efforts. What are your major discoveries in the area of nutrition research?

Dr. KRETCHMER. Our nutrition research efforts deal primarily with the area of human development and focus on maternal and infant nutrition and the effects of malnutrition and undernutrition on the baby. Particularly we are studying mentality and the ability of the child to perform after having been born to a malnourished or undernourished mother.

Our nutrition efforts also focus on very specific aspects of the diet. We are supporting a research project which shows that, in order to make a protein complete, certain amino acids have to be added to it. For example, corn protein is an incomplete protein to which you have to add a molecule called lysine and another, tryptophane, to make it as good a protein as steak. Zinc is also required in the diet. We have supported work in the area of chromium, which has to do with the development of certain enzyme systems described before.

Mr. FLOOD. How do you translate these findings to other programs of the Government concerned with providing meals to children and food supplement to mothers and children and all the other programs?

Dr. KRETCHMER. Our major emphasis has been in the population field and in studies of the low birth weight infant.

I have met with the head of the nutrition programs of the Veterans' Administration and also with the head of the nutrition programs for the Administration on Aging. In the past 6 months I have been speaking to various practitioner organizations, for example, the American Academy of Obstetrics and Gynecology and the American Academy of Pediatrics. Also, we have published articles in the medical and scientific journals, the usual method of information dissemination.

MENTAL RETARDATION

Mr. FLOOD. In your research on mental retardation is that also into the causes of autism?

Dr. KRETCHMER. Autism is an ill defined term.

Mr. FLOOD. There is no doubt about that.

Dr. KRETCHMER. Would our research apply to autism? I would say yes, since autism is an ill defined word and ranges in its simplest form from the child who cannot deal with people to the child whom we might call schizophrenic. I would say any of the research we are doing in mental retardation, which has to do with brain function and the function of the whole child, certainly applies to autism.

LEARNING DISABILITIES

Mr. FLOOD. You mention that you are looking at the problems of learning disabilities along the same line. What do you mean by a learning disability?

Dr. KRETCHMER. It is estimated that learning disabilities afflict 3 million children up to the age of 15 in this Nation. We have research programs that deal with the severely retarded child learning symbolic language so that the child can be taught to communicate.

Mr. FLOOD. You are doing research in the area of learning disabilities.

Dr. KRETCHMER. Yes; on the other end of the spectrum are those children who have learning disabilities in terms of communication

and reading, but in terms of their intelligence, are very bright children. They have specific learning disabilities.

We are doing research in that area, also.

INFANT MORTALITY

Mr. FLOOD. Whenever we ask anybody, "Why is this U.S. infant mortality rate so much higher than some other nations in the world," we are told that other countries have a more homogeneous population, or they say the other countries have a marvelous health insurance scheme that allows for better health care during pregnancy, labor, and delivery and all that.

Do you have any other reasons than the ones I told you about?

Dr. KRETCHMER. I would use those same two reasons. Certainly, we are a heterogeneous population from both a genetic and a socioeconomic point of view. I would also say we could use better health schemes for prenatal care. Regardless of those answers, I would say that our infant mortality rate is intolerable. I don't like it. I consider that the crusade of this Institute is to do something about it.

Mr. FLOOD. Can we conclude, then, from the statements you make that if we passed a national health insurance bill one of the immediate benefits would be a reduction in the infant mortality rate?

Dr. KRETCHMER. Yes; if it were an effective bill.

Mr. FLOOD. I see, and executed, too, right?

Dr. KRETCHMER. Yes; and effectively administered.

DIABETES

Mr. FLOOD. Doctor, you know about the Diabetes Act. That requires most of the Institutes of NIH to put part of their budget into diabetes research. What are you doing in that area?

Dr. KRETCHMER. The NICHD is a member of the National Commission on Diabetes and the Diabetes Mellitus Coordinating Committee, both of which were established under the act.

Mr. FLOOD. How much are you going to invest in that in 1976?

Dr. KRETCHMER. Approximately $1 million.

Mr. FLOOD. Is that a lot?

Dr. KRETCHMER. No; I don't think it is.

NIH MANAGEMENT FUND

Mr. FLOOD. On page 52 of your justifications you show an increase of 28 percent in the payment of that NIH management fund. Now, I have heard all kinds of explanations about pay raises, et cetera. Why is your share of this item increased 28 percent?

Dr. KRETCHMER. The reason for this is really quite simple. We are opening the perinatal biology facility in the clinical center, which is costly.

Mr. FLOOD. Oh, you have an answer, then.

Dr. KRETCHMER. The cost of clinical services relative to the perinatal center are supported through the NIH management fund.

Mr. FLOOD. All right.

Mr. Patten will take over.

SUDDEN INFANT DEATH SYNDROME

Mr. PATTEN [presiding]. I think I am the original sponsor of the Sudden Infant Death Syndrome bill. I take it you feel you have some results?

Dr. KRETCHMER. Yes; I think there have been some remarkable results in the past year.

One is the discovery that crib death babies are not necessarily normal babies. Two, which is more important from a preventive point of view, is that the crib deaths occur during the night invariably and during sleep. We have been able to relate that kind of a finding to periodic breathing. In other words, the child breaths and stops breathing. Obviously if the child stopped breathing for a long enough time, it would die. Third, we have found out that there are peculiarities in the development of the lungs of these children. Our goal is certainly to prevent these deaths and I am optimistic. I think we can do this. We need more information and of course we need a great deal of education.

NUTRITION

Mr. PATTEN. Doctor, this morning on the Today Show they had some movies about malnutrition in the United States. They went to where they were living freely out in the country. Everybody in the picture was so fat. They are living on food stamps, on welfare, and they are healthier than I am. This was the malnutrition program. We saw them eating. I thought they were eating pretty good. I can take them in my district and show real malnutrition, which is not caused by poverty. The senior citizens free lunch program we have in my town is right on the button, Doctor. I know my people. You don't want me to detail it. There are people who have the money but they don't eat right.

You can see so many things that fundamentally must be incorrect. So most of the malnutrition I have seen has no relationship with not having a dollar. It is alcoholism, old age, being alone, mental attitude, avoiding people, sometimes being hard of hearing and avoiding people.

Dr. KRETCHMER. And bad teeth.

Mr. PATTEN. Yes.

They withdraw. You have to seek them. I have an 87-year old man I watch. I have to prod him and take him to a restaurant. He has the money, but you have to prod him to eat breakfast. You know it can be a bad habit which can be cumulative, too. I can tell you that our senior citizens groups try to educate the people on how to get the best use out of the food and what foods to eat, and they hand out these mimeographed sheets on nutrition. Some things do filter through in the field of nutrition.

Well, it would be nice to talk of so many things. You say that in 6 months you have had stimulus and challenges.

Dr. KRETCHMER. Yes; I said it has been intellectually rewarding.

Mr. PATTEN. When I was in Hungary, they told me they had the lowest birth rate in the world. I went to one of their nurseries and it was immaculately clean. The women said to me, "Who would bring

a child into the world in this country?" That is actually what she said to me. She was a lovely woman caring for the babies.

Mr. PATTEN. Mr. Michel.

TRAVEL

Mr. MICHEL. You show a 1976 budget estimate of $276,000 for travel and transportation of persons which is only $17,000 below last year's budget. That's quite a bit of money for travel expenses—what kind of activity is involved here?

Dr. KRETCHMER. The two primary areas of travel performed by the Institute are: for the review, monitoring, and negotiation of grants and contracts; and for attendance at professional meetings both for the dissemination of information to the scientific community, practicing physicians, and the general public and for our staff to gather new knowledge. The travel budget also includes funds for our intramural scientists to go to other laboratories for training in the latest technology. We are constantly evaluating this area for the most effective use of these funds.

POPULATION RESEARCH

Mr. MICHEL. I noted in your justifications that one of your completed investigations found that "relative to income, the cost of children is less the higher the income." Now, it seems to me that conclusion is pretty logical and I would guess that's the case and I haven't had the benefit of any study to base my conclusions on. How do you justify spending money on these kinds of projects? What is the return for the money—and just how much money was spent on this study?

Dr. KRETCHMER. This finding is only one small aspect of the results of a large number of studies funded under a grant to Dr. Kingsley Davis of the University of California at Berkeley. This research deals with the social and economic factors influencing reproductive behavior. This particular finding emphasizes the importance of small family size to low-income groups.

The research project was funded for a 5-year period, beginning in November 1969, at a total cost of approximately $300,000. The work has been highly productive. Dr. Davis and his colleagues have published many papers based on the research supported by the grant.

RESEARCH GRANTS

Mr. MICHEL. You show over $60 million for research grants, competing and noncompeting, which have been completed, are completing, or are terminated. How much accounts for those completed here? That is pretty much the same question I have asked in the other area.

Dr. KRETCHMER. Mr. Miller can provide that information.

Mr. MILLER. In the noncompeting category we will have about 180 grants being completed or converting to competing status. These grants are funded at about $12½ million.

Mr. MICHEL. Would it be too difficult to give us some exposition of what we have realized from those?

Dr. KRETCHMER. I think the Congress deserves such an explanation, but I would like to ask if we could do it briefly in a general summary statement.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT—ACCOMPLISHMENTS FROM COMPLETED GRANTS

The accomplishments of the National Institute of Child Health and Human Development noncompeting regular research grants being completed in 1976 are too numerous to enumerate in detail. Examples of these accomplishments follow:

POPULATION

In population research, the grants being completed represent a cross section of the major areas: fundamental research in reproductive biology, contraceptive development, contraceptive evaluation, and social and behavioral sciences.

Grants in fundamental research in reproductive biology have supported studies to elucidate the mechanisms of hormone action and to control sperm production. In the areas of contraceptive development and evaluation, studies were conducted to determine the risk factors of oral contraceptives as related to hypertension.

A simple chemical has been found in the blastocyte (early embryo) which blocks ovulation. Its structure has been determined and it has now been synthesized in the laboratory. It has potential use as a contraceptive. The metabolism of steroid hormones has been shown to occur in the brain, and this has important implications for reproductive functions and also behavior.

The social and behavioral sciences research has examined the changing patterns of fertility. Predictions of failures in contraceptive planning have also been studied.

PERINATAL BIOLOGY AND INFANT MORTALITY

The grants being completed in 1976 studied maternal physiology and complications of pregnancy, labor and the birth process, pathophysiology of the developing fetus and congenital malformations, newborns at high risk and the sudden infant death syndrome.

Maternal physiology was studied by a project of exercise hemodynamics and respiration in pregnancy which has produced valuable information on the effect of exercise on maternal oxygen consumption, the magnitude and distribution of cardiac output, uterine blood flow, and fetal oxygenation.

Labor and birth process was studied by continuous monitoring of cervical dilation and fetal descent by a special instrument to establish whether a relationship exists between fetal heart rate and changes in uterine contractions.

To gain a better understanding of the pathogenesis of neonatal hypocalcemia, studies are in progress to explore endocrine factors involved in neonatal calcium metabolism. Information has been obtained to show the mechanisms involved within and between tissue components in the limb development of the fetus. Useful information is also being obtained on minor birth defects attributed to teratogenic factors of the environment.

To enhance our understanding of the biochemistry of placental development and function, information concerning the effects of various protein hormones on the growth and cell division and on various molecular parameters have been established.

Such studies lead to indentification of infants at high risk and to understanding of the causes of the sudden infant death syndrome.

MENTAL RETARDATION

The grants being completed in 1976 were concerned with the detection, prevention, and amelioration of mental retardation.

Several projects that studied chromosomal abnormalities led to the development of a new cytogenic technique to provide a more precise characterization of chromosomal abnormalities, and increased our knowledge of how chromosomal abnormalities affect the phenotype in relation to spatial and numerical abilities, and verbal and nonverbal abilities.

The organic metabolites excreted in urine by normal babies were studied by gas chromatographic-mass spectrometric methods to establish a norm for the

amount of specific metabolite levels and various disease states. Another study of patients with Charcot-Marie-Tooth syndrome, progressive neuropathic muscular atrophy, has developed a new clinical technique and provided useful information relevant to understanding disease processes in man.

Studies were conducted to develop better methods for ameliorating the deficiencies of mentally retarded children in learning retention, and a variety of cognitive processes.

GROWTH AND DEVELOPMENT

The grants being completed in 1976 fall across the four major problem areas of the growth and development program: nutrition and malnutrition, learning disabilities, the impact of childhood illness on later development, and growth and physiologic maturation.

In the area of nutrition, for example, the program supported studies of the relationship between nutrition and physical development in rural areas and the interaction of both nutrition and social stimulation in effecting competence in children.

In the area of learning disabilities, we supported such studies as how memory operates in children and adults, how children develop spatial perception, how children learn to control the stimulus in a learning situation, and how children learn to use language.

Studies of the impact of childhood disease in development include the following: the effects of shock in infancy both on the child's metabolism and hemodynamic blood system; how genetic childhood disease affects the aging process; how the humoral and cellular immune responses develop; and clinical and laboratory studies of rubella, German measles.

Finally, in physical growth, studies were conducted and published on the mechanisms controlling the growth rate. Predictions can now be made about the ultimate physical stature of both normal and deviant children. More importantly, interventions can now be undertaken to modify the growth rate in deviant cases.

Mr. MICHEL. The reason I asked specific numbers was whether or not my request was reasonable or unreasonable. In the area of aging, I think it is a reasonable request so give me something for all 12. Here, use a little discretion. I don't want just a lot of fanfare in the record.

Mr. CONTE. Will you yield?

Mr. MICHEL. Yes.

Mr. CONTE. The chairman asked you the question this morning on what happened with the $20 million cut in your budget. If I correctly remember, you answered by saying you would be short $20 million in grants, is that right?

Dr. KRETCHMER. No, sir; I was more explicit than that.

Mr. CONTE. Well, let me finish. Didn't you say it would cut out 327 grants?

Dr. KRETCHMER. Yes, in the noncompeting category.

Mr. CONTE. Three hundred and twenty-seven grants?

Dr. KRETCHMER. Yes, sir.

Mr. CONTE. Could you for the record tell us what those 327 grants are and where they would go and how much each grant costs?

Dr. KRETCHMER. We could try, Mr. Conte.

Mr. MICHEL. Would that have been decided?

Dr. KRETCHMER. These figures are all estimated, so the 327 grants would not be specifically determined.

Mr. MICHEL. Here you are asking for the money. You went to the OMB for the money and you must have had some idea where it was going. You were very specific this morning in saying it was 327 grants, so you must have had some idea of where those grants were going.

Dr. KRETCHMER. I think it is perfectly reasonable to ask the question

both of you are asking. However, because of the number of grants involved, I would like to respond to this question in general program categories.

In other words, I would report what we are not going to be doing in areas such as pregnancy and infancy in a summary statement. There are 327 grants involved here, an enormous package. I will be happy to supply additional information for the record.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT—AREAS OF RESEARCH AFFECTED BY TERMINATION OF NONCOMPETING RESEARCH GRANTS

In order to achieve the suggested reduction of funds in 1976, the National Institute of Child Health and Human Development would terminate approximately $20 million of noncompeting grants. Such reduction would raise the fundable priority score to a very high level and thus, middle-range priorities would have to be discontinued. These grants often represent innovative ideas and approaches that, because of the risk associated with the new ideas, have not received the highest scores.

POPULATION

The decrease would affect the entire range of population research, from basic biology to social demography.

Examples of grant terminations would include research on the molecular biology of the reproductive processes, demography, and demography and human ecology. Other studies on reproductive endocrinology and gametogenesis and reproductive biology would also be terminated. These kinds of research are important to the development of new contraceptive methods—which allow for safe and effective family planning—and to understanding of the social and psychological determinants of the birth rate, or factors affecting how people decide on the numbers and spacing of their children.

PERINATAL BIOLOGY AND INFANT MORTALITY

To achieve the reduction of funds it would be necessary to terminate noncompeting regular research grants on a priority basis of those funded within the last year or two.

Two of the major areas of research that would be affected concern maternal health and fetal development, including studies designed to explore important problems such as why labor begins, complications of diabetic pregnancy, impact of maternal infection on fetal development and infant well-being, and causes of sensory and neurologic impediment in the newborn. Other studies which would terminate relate to our understanding of why some infants succumb to the sudden infant death syndrome (crib death); causes of birth defects; and causes of premature birth and retardation of growth in the developing fetus.

MENTAL RETARDATION

The termination of noncompeting research grants would affect the biomedical, behavioral, and interdisciplinary studies of mental retardation.

The biomedical studies terminated would include cytogenetic studies on chromosomal aberrations such as found in Down's syndrome, mongolism, research on the effect of cytomegalovirus on the developing nervous system, and several investigations to develop methods for antenatal diagnosis of anencephaly and spina bifida and the role of inheritance in their determination.

Behavioral studies concerned with a wide range of variables influencing the development and functioning of retarded individuals would be terminated. Research concerned with memory, cognition, and motivation and how these are altered by the training and living conditions of the mentally retarded would be affected. Other behavioral studies that would be curtailed include research on parent teaching styles, the epidemiology of mental retardation, and the improving of communication in retarded children.

Some examples of the interdisciplinary projects that would be affected are autism, control of social behavior, neurological disorders, and factors affecting prenatal and postnatal nervous system development.

GROWTH AND DEVELOPMENT

The termination of noncompeting research grants would affect all the areas of the growth and development program: nutrition and malnutrition, learning disabilities, the impact of childhood illness on later development, and growth and physiologic maturation. Studies would be curtailed on the relationship between nutrition and physical development, and the interaction of nutrition and social stimuli to affect competence in children. Research would be slowed in the area of the operation of memory, the development of spatial perception, and the language learning process.

The reduction would affect studies on the effect of genetic childhood disease on the maturation process, the development of the immune response, and clinical and laboratory studies of rubella. The reduction would postpone attempts to modify the growth rate in cases where a child's stature deviates substantially from the norm.

Mr. MICHEL. I will tell you why I am a little squeamish, even though I would like to have as much information as I can anytime I ask for it. There can be the temptation or the kind of precedent set where you are telling yourself particular grants that obviously fan out around the country, and then the pressure is built up on each and every one of us to raise the figure to accommodate my grant in Peoria, his grant in Pittsfield, and there can be an additional number submitted and we can get the whipsaw treatment. I just don't like to find myself put in that kind of box each time we take the bill to the floor, as much as I can appreciate my colleague's desire to know whether or not there will be sufficient funds in here conceivably to take care of whatever grant applications might have been submitted from his district, my district, the chairman's, or anybody else's.

Mr. CONTE. I would like to have it, but my reason for wanting it was altogether different. You know what is going to happen. There will be a move to put in the $20 million. I would like to know whether we can get by without the $20 million and whether those grants are really essential to carry on this particular work.

Mr. MICHEL. Right. But I think the Doctor indicated that he could respond in a general way. I think you gather from reading between the lines of the line of questioning, if I might use that terminology, that we do have some serious questions about some of the directions even your very knowledgeable people go in.

Dr. KRETCHMER. I would like to make one point here that I did not make clearly before. I mentioned the 327 grants and the $19.4 million they would require in response to Mr. Conte's question: We would in fact break our commitment of about $20 million in not paying those 327 grants. In other words, what we discussed before was a 3-year or a 5-year commitment. We would break this commitment at 2 or 3 years, rather than continuing support for work that is going along well and in accordance with what the investigator said he or she would do.

So these 327 are not new grants. It is the noncompetitive category we are talking about. That would mean that we would reduce our funding of noncompeting grants to a figure of 63 percent of the requirement, in contrast to all other years when we have been able to pay them 100 percent.

Dr. LAMONT-HAVERS. Mr. Michel, I think it should be made clear that the justification tables are based on very specific guidelines. One such instruction was that the amount in the President's budget for

competing grants would stay. At NIH we would be extremely loath to move in and cut out commitments. I think that would be dreadful. I think it is more than likely that when we came to administer the fiscal 1976 budget at this level, we would then readjust the amount which we would assign for competing grants in order to put more into noncompeting. Therefore, the list which we could give you regarding the projects which would be identified under these guidelines would probably not match the actual list for phase out when we actually came to seeing how we wanted to distribute that money properly.

I think it would do more harm to the biomedical community to keep that competing figure sacrosanct at the expense of the noncompeting projects where institutions, and individuals, have been committed.

As far as they are concerned, the grantee institutions have committed their resources, but we could not follow through.

Mr. MICHEL. One question I have, in the extreme, you could play the game of putting all the money in noncompeting grants in a given year and then the Congress would be in a position, 'Oh, but we are not doing anything new; therefore, we have to put in 30, 40, or 50 million more," and of course, it can be a game that gets played and again I am caught in between. I have to take your good judgment, that you in the scientific community will make a good rational judgment between what is more important, given the amount of limited resources in that year to go the route of competing or noncompeting grants.

Dr. LAMONT-HAVERS. This is quite true. I think, though, that it is very difficult for us to fine tune that amount of money now.

TITLES OF RESEARCH PROJECTS

Mr. MICHEL. I have some other questions that I will submit for the record, because I do not want to take too much time. There is another area, though, that I would like to have a personal response on. That is that we have this index in the office of the research grants funded by the various Institutes. I might say that this last week we had a spirited debate over on the floor with the National Science Foundation's projects and the ridicule that some Members of Congress were getting for the kind of titles, if nothing else, that were attached to some of them.

I made some rather uncomplimentary remarks on the floor, although I admitted that I don't consider myself a scientist or an academician. et cetera. I said we have to trust the pros. But they have to understand that we are the ones taking the heat from the general public.

This morning I got a letter from a doctor of science taking exception to some of the things I said on the floor of the House at the time. He really didn't quite get focused in on the issue I was trying to make.

I have to make it with you, too, and your colleagues out at NIH. Some of the grants attributed to your Institute include a title, "Developing Competence in Standard English." Another is "Beginning and Fluent Reading," I would have to ask if these projects aren't more reasonably Office of Education programs, particularly when we have the National Institute of Education, and that has been a controversial thing, and they say that is where the research is going to be housed under one roof.

Dr. KRETCHMER. I think one could take your point of view on that subject. Another approach which I would more likely take is that we have a mandated concern for mental retardation and subnormality. The two areas of reading and language are really very important in this particular field. Because this work is conducted on a really scientfic basis, I would say this a reasonable and important area for our Institute to be concerned with.

Mr. MICHEL. That is a good explanation for that. That satisfies me. Now a project entitled, "Culture, Religion, and Personality in Southeast Asia." Does that have a bearing in your shop?

Dr. KRETCHMER. Most of the money in population research is spent by the National Institute of Child Health and Human Development. We have a concern in this Nation, not only for ourselves, but for the nations of the world. Understanding culture and religion applies not only to our work in the area of population dynamics, but also to our concerns for maternal and infant nutrition because we cannot force people to eat steak, for example, when it is not within their religion or culture.

So I would defend that study as being important to our Institute.

Mr. MICHEL. Another, "A Grant for Conference on Family Bureaucracy in North Carolina." Here I fear that we end up with a bureaucracy investigating another. What is the process by which money is allocated for these activities, and who is responsible for monitoring the activities of a project like this?

Dr. KRETCHMER. I am not thoroughly familiar with that project, but I think I can defend it from the title in terms of our interest in the family, the spacing of children, and problems of that order.

The smallest bureaucratic element in society would be the family. How decisions are made within the family in terms of childbearing and problems along that order are important. The results of this conference will probably be published and therefore disseminated to the general public.

Mr. MICHEL. In the interest of time, then, that is all I have personally, but please expand on that one in the record a little bit because I emphasize again, we have to take some unmerciful heat in our districts. We like to pride ourselves in telling the people that we are going over these line items very carefully. Every day we are doing this. Obviously we cannot touch them all to the degree that we would like, but we have to rely on you folks to keep us out of hot water from time to time, too. I hope you appreciate our problem.

Dr. KRETCHMER. Certainly.

[The information follows:]

NATIONAL INSTITUTE ON AGING—"CONFERENCE ON OLDER FAMILY AND BUREAUCRACY"

The exact title of the grant referred to is "Conference on Older Family and Bureaucracy." The grant was awarded to Dr. Ethel Shanas of the Gerontological Society. The conference was held at Duke University, N.C. The purpose of the conference was to contribute to our knowledge about the older family, in particular how the older members relate to the younger and to various social systems The conferees examined the methods by which the kinship network operates to link the aged with society and its organization systems and how such systems affect the quality of relationships between the aged and their families. Constraints and supports for the elderly as found in the social system

were considered. Among these were patterns of financial care, work and leisure, health care, living arrangements and housing and social services. Little is known about the quality of interaction between old people and their families, immediate and extended, and with the service systems to which old people relate, or what the function of this interaction is within societies.

Dr. LAMONT-HAVERS. The Child Health Institute also supports the project discussed recently about the relationship of the baby monkey to female dog. This is an extremely important project in the study of child development.

POPULATION RESEARCH

Mr. FLOOD. Mr. Obey.

Mr. OBEY. Could you give me some description again of the kind of research you are doing on population control, contraception, especially the safety aspects of that problem?

Dr. KRETCHMER. There are three aspects to our research in contraception. One is the development and evaluation of new contraceptives for both males and females. There is a good deal of research going on in this area.

The second portion of our contraceptive research is just what you have put your finger on, the safety of contraceptives. There is a good deal of work going on regarding changing molecules so that lower doses can be given and some of the side effects be avoided.

Mr. OBEY. How much are you spending specifically on research into the safety of contraceptives?

Dr. KRETCHMER. I will have to ask Mr. Miller for that information. While he is looking for that figure, may I go on?

Mr. OBEY. Surely.

Dr. KRETCHMER. The third area is the area we call basic biomedical research and reproductive biology. That is devoted to learning about the mechanisms of reproductive biology, production of the ovum and sperm, and hormones that regulate these two cells. In the contraceptive evaluation area for 1976 we expect to spend $4.5 million.

Mr. OBEY. How much were you spending 3 years ago?

Mr. MILLER. In 1972, we were spending about $5 million in this area.

Mr. OBEY. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Conte.

Mr. CONTE. In regard to family planning, are you the only agency involved in research on that?

Dr. KRETCHMER. No; we are not the only agency. We have prepared a report mentioning a number of other agencies involved. Within DHEW is the Deputy Assistant Secretary for Population Affairs. I think it would be reasonable to consider him and his staff an agency. The Agency for International Development at the Department of State is concerned with family planning in foreign countries. The FDA is also involved in family planning. There are other agencies, too. Between AID, the Deputy Assistant Secretary for Population Affairs, and the NICHD, we cover most of the research in family planning.

Mr. CONTE. Mr. Obey and I serve on the Foreign Aid Committee. We appropriated $115 million for family planning in 1975. Most of that program is overseas, but not all of it. They have a program at Harvard which I checked into costing nearly $30,000 per student. They bring students over here to train them in family planning. They

also have some experimental programs. Then you have the foundations, also, which you failed to mention. I imagine the Ford Foundation and Rockefeller Foundation and Carnegie Foundation and other foundations are also working in this particular area. Maybe you have somebody in your shop who can pull all of this together and give us some kind of a figure of how much money is spent in the United States on family planning.

Dr. KRETCHMER. The figure probably has been pulled together by the Planned Parenthood organization and we could surely submit it. I should indicate also that there is an Inter-Agency Committee on Population Research which Dr. Corfman, the Director of the Center for Population Research, heads and which reports to the Deputy Assistant Secretary for Population Affairs. I have a table in front of me which is population research projects supported by Federal agencies. For example, the Agency for International Development is listed here for about $4 million with 54 projects in the research area. I know some of the research they are doing, for example, in Nigeria. The Department of Health, Education, and Welfare, including the NICHD, is listed for $55 million with 729 projects. So we do have some figures pulled together for Federal agencies.

But this is only federally supported research. You have also requested private agencies which would include, particularly, the Ford Foundation, Rockefeller Foundation, and the Population Council.

[The information follows:]

FUNDING FOR FAMILY PLANNING RESEARCH

The best data available for the funding of family planning research show that the United States spent approximately $75 million in 1974. The public funding, principally at the Federal level, totaled $61.7 million. Most of the Federal support, $51 million, was provided by the National Institute of Child Health and Human Development. The latest private funding estimate approximated $13.3 million, most of which was attributed to three major organizations: the Ford Foundation, $7.6 million; the Population Council, $3 million; and the Rockefeller Foundation, $2.1 million. It should be noted, however, that much of the grant program sponsored by the Population Council was financed by the Ford and Rockefeller Foundations.

Mr. CONTE. Right.

You mentioned on page 5, "At the same time because we have been particularly concerned about the relationship of contraceptives and congenital malformations, we are developing projects to explore indications that use of oral contraceptives during the early part of pregnancy is associated with malformations of heart and limbs. Are there any other forms of contraception that you have found that have an adverse effect on the child?

Dr. KRETCHMER. The way that sentence is worded implies from a scientific point of view that there have been indications. There have been really no supporting data to show or to prove that oral contraception is related to malformations of hearts or limbs. Where the data were very clear, such as in the Thalidomide story, there was a very clear association between a sedative taken early in pregnancy and development of the malformations. If from a scientific point of view there were a clear relationship between the oral contraceptive and the development of malformations, we would see many cases as we did with Thalidomide, coming up here and there. We are work-

ing closely with the FDA on this particular problem as well as in the field with investigators and surveillance methodologies.

In the State of California there is a project which is constantly watching about 17,000 women who are using oral contraceptives.

Mr. CONTE. How about the clinical trials of contraceptive agents for men? Can you tell us whether there have been any adverse effects associated with contraceptive agents for men?

Dr. KRETCHMER. First, I might spend 1 minute on explanation of mechanisms. There is a set of hormones, one produced by the pituitary gland which stimulates various cells in the testes, and another produced by the adrenal gland, so there is the usual type of balance throughout the body. These hormones have to be transported in the blood to stimulate the two cells in the testes that would be involved, one in the production of sperm and secondly the fostering of sperm from where it is to where it is going to be.

The male contraceptive research is aimed at disturbing that transport system just as you would disturb a railroad by pulling out a piece of track. This is being worked on now and it looks like it is fairly effective. There have been no side effects.

Mr. CONTE. This would seem to be one of the most encouraging breakthroughs I could imagine.

Dr. KRETCHMER. Personally, I think it is very exciting.

Mr. CONTE. Do you have any studies showing that abortion on a woman has any effect on the child later on if she wants to give birth to a child and whether there is any effect on that child?

Dr. KRETCHMER. We are conducting studies showing the effects of abortion, and the motivation for abortion both in the physician and the woman herself. They are not far enough along to answer your question. So far we have not seen any effects.

To put an appendix on my answer, if we are going to look at the whole mechanism, we have to look at not only physiological effects but also psychological effects. That is how those studies are designed, to look at the whole woman and the following baby.

Mr. CONTE. I am thinking about the following baby, whether there will be any after effects as you cite here with contraceptives.

Dr. KRETCHMER. This is an area we are pursuing.

HUMAN SUFFERING AND ECONOMIC LOSS

Mr. CONTE. You said you will be focusing in those areas which cause most human suffering and greatest economic loss. Could you provide us with a list of these highest priority areas along with their economic cost?

Dr. KRETCHMER. Yes, sir, I would like to do that. If I may, I would like to say a couple of sentences now.

Mr. CONTE. Surely.

Dr. KRETCHMER. I believe that problems that begin early in life and carry throughout life are of an inestimable cost. For example, the cost of the premature infant in the United States is approximately $1 billion a year. I can give you the figures that there are about 150,000 of these babies that are given long-term care in a hospital at the rate of $250 to $300 a day. They usually stay in a hospital 30 days. That figure comes to about $800 million a year.

What is not in those figures is that from those premature infants we are going to have a body of 40,000 to 50,000 children who throughout their lives are going to suffer from severe disabilities, like mental retardation, or what you can consider minor disabilities, such as crossed eyes or even eye blindness. The costs of that to society are almost inestimable, but the expense carries throughout a whole lifespan.

The subject of crossed eyes brings about the problem of learning disabilities, because the child does not read as well. This has to be a high priority area for the National Institute of Child Health and Human Development because there is human suffering for the individual and family, and the cost of human suffering is inestimable.

I have given you the premature infant figure, but that is only the cost of the baby's care in the hospital. Then the costs accrue as you go through disabilities. I think if we work hard enough, well enough, and intelligently enough, we could prevent premature births and with them the fiscal losses, which are minor when compared with human suffering.

Mr. CONTE. You can put more in the record.

[The information follows:]

ECONOMIC IMPACT OF CERTAIN PROBLEMS OF HUMAN SUFFERING

Low birth weight infants, those who weigh 5½ pounds or less, are a major source of chronic developmental disorders. These infants fall into two categories: those who are born too soon and those who are born too small. Of the approximately one-quarter million babies born in these categories in 1973, about 40,000 died within the first month of life and these infants accounted for about 95 percent of all babies who died in this period.

In addition to being the principal source of neonatal mortality, low birth weight infants who survive have the highest probability of being among the estimated 6 million victims of mental retardation; the 1 million who suffer from epilepsy; and the three-quarter million who have cerebral palsy. It is estimated that while the costs of care for premature infants in hospital approaches $1 billion, costs of care that accrue over the lifetime of these infants because of expenditures for intermittent hospital care, special education, and specialized neurologic therapy, could exceed another billion dollars. The cost to society in terms of lost productivity and taxes is inestimable.

COMMUNICATIVE DISABILITIES

Mr. CONTE. You mentioned a study about communicative disabilities. Isn't a great deal of research being done on this in the Neurological Institute? Do you coordinate your research with them?

Does it overlap or duplicate?

Dr. KRETCHMER. Yes, the National Institute of Neurological and Communicative Diseases and Stroke and the National Institute of Child Health and Human Development do coordinate their activities.

We are interested in learning disorders as they relate to the premature child. We have brought out as one of our primary initiatives the problem of the low birth weight infant. Through Dr. Lamont-Havers' efforts an interinstitute coordinating committee at NIH has been formed to deal with the question of gaps or duplications between institutes.

SUDDEN INFANT DEATH SYNDROME

Mr. CONTE. You outlined your work in the area of sudden infant death syndrome. How much will you spend this year and how does it compare with what you spent last year? What has been accomplished in SIDS during last year?

Dr. KRETCHMER. In fiscal 1976 we will spend $4.7 million in SIDS. In fiscal 1975 we will spend $5.2 million. The major advances that have occurred in the past year have been, I think, rather surprising ones. We have found that the crib death infants were not totally well. In one way or another they suffered from stress. We had an inkling of this when we found that many of these infants had been premature. Second, we found that SIDS occurs mainly during sleep and is probably associated with physiological sleep phenomena, particularly periodic breathing.

Third, we found that there have been changes in the small vessels of the lung in these infants who succumb to sudden infant death. As has been explained in previous years, we have sponsored over a dozen research workshops to stimulate researchers who had not been involved in SIDS to enter that particular area. We also had a meeting last August concerning dissemination of information.

We have another coordinating meeting coming up in June.

POPULATION RESEARCH

Mr. CONTE. I touched on the foreign operations budget for population research. I would like to know what portions of your research in the center for population research might be applicable to developing countries and would you outline some recent work of the center which might be applicable to population control overseas?

Dr. KRETCHMER. We would be glad to submit a full report of that for the record.

National Institutes of Health

Summary of Programs Related to Population Research and Family Planning

The research programs of the Department in the population sciences are directed by the National Institute of Child Health and Human Development. Section 444 of the Public Health Service Act authorizes the Institute to conduct and support research and training relating to maternal health, child health, and human development, including research and research training in the special health problems and requirements of mothers and children and in the basic sciences relating to the processes of human growth and development, including prenatal development.

Section 1004 of Public Law 91-572, "The Family Planning Services and Population Research Act of 1970," authorizes the Secretary of Health, Education, and Welfare to make grants and to enter into contracts "...to promote research in the biomedical, contraceptive development, behavioral, and program implementation fields related to family planning and population..." Expenditures by the Institute in fiscal year 1974 for population research were $51.0 million. They are projected to be $51.0 million for fiscal year 1975.

Other components of the National Institutes of Health provided $7.3 million in fiscal year 1974 to support a variety of extramural activities with important implications for population research. Research in reproductive endocrinology supported by the National Institute of Arthritis and Metabolic Diseases totalled approximately $2.8 million in fiscal year 1974. These studies provide basic information essential in the development of new methods for controlling reproductive processes. The National Cancer Institute's interests in reproductive endocrinology, other reproductive processes, and carcinogenic effects of synthetic estrogens are relevant to understanding normal function and fertility control. In fiscal year 1974, $1.7 million was spent to support these studies.

The National Heart and Lung Institute awarded $0.4 million for studies of the effects of estrogens, progestogens, and steroid contraceptives on blood clotting mechanisms and the physiology of circulation. Several studies in reproductive neuroendocrinology and genetic aspects of reproduction were supported by the National Institute of Neurological Diseases and Stroke and the National Institute of General Medical Sciences, respectively. Support for population research in these two Institutes totalled about $0.2 million in fiscal year 1974. The Division of Research Resources administers approximately $2.3 million in general research support relevant to the population field.

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National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) and its Center for Population Research (CPR) have primary responsibility for the Federal effort in population research. This report describes research on the development of new means of fertility regulation, the evaluation of contraceptive methods currently in use, and the analysis of social and behavioral determinants and consequences of population size, composition, and distribution. It also discusses the NICHD effort in fundamental research in reproductive biology and the social sciences, upon which advances in contraceptive development and the solution to population problems are dependent. Finally, it describes the Institute's program to support institutions, develop scientific manpower, facilitate the coordination of Federal population research programs, and disseminate population research information.

A. Biomedical Research

1. Contraceptive Development

The contraceptive development program involves research aimed at new approaches to fertility regulation. During fiscal year 1974, important developments have taken place in this program.

a. Drug Development

Drug Synthesis Program. The efforts to produce better chemical contraceptives for both men apd women have continued with increasing intensity. The chemical synthesis and the biological evaluation programs have cooperated closely in exploring the contraceptive utility of new chemical entities.

Estrogens (female sex hormones) are potent antifertility agents, constituting an essential component of most currently marketed oral contraceptives. However, estrogens are frequently associated with unpleasant side effects, and, in a few women, present real health hazards.

One aim of the drug synthesis program is to separate the antifertility activity of estrogens from their unpleasant side effects. In this connection, a class of compounds related to estrogen appears promising. Studies are underway in two species of primates to assess the clinical potential of two of these compounds. Information relating to these studies will be available during fiscal year 1975. If promising results are obtained, preclinical drug safety studies will be initiated which will allow their evaluation in man. Within the same class of compounds, work is in progress to find modifications having even greater separations of antifertility activity from undesirable side effects.

Inhibitors of the luteinizing hormone releasing factor (LRF) which are intended to block ovulation have been synthesized and evaluated for biological activity. Even though presently available compounds delay ovulation, their contraceptive utility is limited by their rapid inactivation in the body. Current research involves attempts to develop methods for extending the biological life of these compounds through chemical modifications and through incorporating them into biodegradable drug delivery systems.

Biological Drug Testing Facilities. Compounds from the drug synthesis program, as well as compounds from other sources, are evaluated for their contraceptive utility at a drug testing facility under contract to the program. The biological testing facility is also utilized to evaluate drug delivery systems. To optimize advanced stages of the drug development program, the CPR has contracted for a new primate (baboon) facility. The present primary aim of this primate facility is to assess the contraceptive efficacy of synthetic estrogens.

New Uses of Existing Drugs. Studies on the safety and efficacy of ethynyl estradiol and conjugated natural estrogens for post-coital contraception are being conducted at four U.S. clinics. While no major problems have been encountered, the incidence of nausea and vomiting is high but can be controlled satisfactorily with anti-emetics. Pregnancies occurred in two women who started ethynyl estradiol medication between 48 and 72 hours following unprotected midcycle coitus. This may indicate the necessity for instituting treatment within 48 hours of exposure for maximum contraceptive efficacy.

Male Contraception. During fiscal year 1975, the NICHD will conduct additional clinical trials to evaluate the contraceptive efficacy and safety of synthetic male hormones. At the laboratory level, activities in male contraception involve (1) synthesis of new androgens (male sex hormones), (2) synthesis of known androgens and their evaluation as male contraceptives, (3) investigation of new drug delivery systems for the maintenance of steady drug levels in the body, and (4) exploration of potential new target sites for contraceptive interference.

The initial clinical trial of chemical contraceptives for men has been completed. This work involved the daily oral administration of a weak synthetic male hormone combined with a once-a-month injection of a potent synthetic male hormone. In most men, sperm numbers decreased significantly after two months of therapy. Such low sperm numbers are considered incompatible with fertility. Sperm numbers returned to normal approximately six weeks after cessation of the therapy. None of the men exhibited undesirable side effects, which lends support to the feasibility of this approach. Future plans call for the expansion of these studies and the search for new chemicals.

b. Device and Systems Development

Drug Delivery Systems. The development of new drug delivery systems has progressed steadily. The aim of this program is to develop biodegradable polymers within which contraceptive drugs may be placed. Theoretically, such a system could deliver the drug at a predetermined steady rate over extended periods of time, eliminating the necessity for daily administration. Since the polymer would degrade slowly in the body to harmless constituents, it would not have to be removed after the drug had been exhausted. Several polymers have been formulated and are being evaluated in vitro and in animals. The drugs being used in the drug delivery systems represent both currently marketed oral contraceptives and experimental drugs from the drug synthesis program.

Long-Acting Injectable. The need for contraceptive methods which would free women from daily pill-taking or other forms of self-medication related to the menstrual cycle or to the time of sexual exposure has been recognized for many years. Long-acting (three to six months) injectable drugs are one potentially promising means for achieving this goal. While several injectables have undergone extensive laboratory and clinical testing, none has reached the U.S. marketplace.

During fiscal year 1975, the NICHD will let a contract for the evaluation of one promising long-acting injectable contraceptive. This long-term project will incorporate the animal studies and clinical trials required by the Food and Drug Administration.

Devices. Two new intrauterine devices (IUDs) are presently being evaluated. An IUD which releases small amounts of the female sex hormone, estriol, has been evaluated in the rabbit. The device without the hormone has no effect on fertility, whereas the device releasing estriol is highly effective. This IUD is being tested in baboons to establish the level of the drug that could be released in the uterine cavity without affecting other body organs.

A soft fluid-filled IUD has been tested in one hundred women volunteers with initial encouraging results. As a consequence, the testing program is being expanded to an additional two hundred subjects. Plans are being developed to compare this IUD to presently marketed IUDs in simultaneous clinical trials.

An instrument known as a steerable hysteroscope is undergoing initial clinical trials in women scheduled for elective hysterectomy. The instrument provides operative access to the openings of the fallopian tubes into the uterus under direct visualization. A series of occlusive devices (tubal plugs) now undergoing evaluation in the baboon will undergo clinical trial in the near future. The hysteroscope will be utilized in the insertion of these plugs. The instrument may also be helpful in the diagnosis and removal of discrete tumors of the uterine wall. By enabling the surgeon to see the inside of the uterine cavity in a safe manner, the hysteroscope could prove to be a valuable tool in the development of new fertility regulating methods.

The device program is also aimed at making vasectomies or vasal occlusions readily reversible. Several types of devices are undergoing extensive evaluation in a variety of laboratory animals, and successful reversal of infertility to fertility has been accomplished. During fiscal year 1975, a decision will be made concerning the feasibility of this approach to human fertility regulation.

c. Directed Fundamental Research

The directed fundamental research portion of the contraceptive development program is devoted to studying those basic research areas which appear most likely to lead to significant new methods. Such areas include the following:

Oviductal Motility and Ovulation. The transducer development program has produced sophisticated instrumentation for measurement of the muscular forces required for transport of eggs through the oviduct. Some transducers can detect the presence of freshly ovulated eggs in the oviduct, thereby indirectly signalling the time of ovulation. Use of this instrumentation enables investigators to expand the fundamental knowledge of reproductive function upon which new contraceptive approaches can be based.

Tissue-Hormone Interaction. The ability of reproductive hormones to interact with specialized cell components, called receptors, has been extensively explored and is dealt with more fully in the section describing fundamental research activities of the NICHD. These receptors have been isolated in a relatively pure form and utilized as a test system to measure the circulating levels of hormones. Recently it has been shown that such systems can be utilized for pregnancy determination or for the rapid biological evaluation of new drugs. The receptor studies serve as a good example of the translation of fundamental biomedical research into applied sciences.

Sperm Enzymes. Sperm contain enzymes which are required for fertilization. Intensive efforts are underway to identify, isolate, and purify these enzymes. Ascertaining the biochemical characteristics of these enzymes and discovering whether they are unique to sperm could lead to the development of specific enzyme inhibitors which would block fertilization.

2. Fundamental Biomedical Research

The goals of this program, which is the largest single CPR activity, are to expand our understanding of mammalian reproductive processes and to increase the knowledge base essential for such significant technological advances as new contraceptives. This work represents a necessary long-term investment in the mission of CPR.

The basic research projects which may provide the most significant new leads for contraceptive development in the near future are those aimed at elucidating the mechanism of action of hormones in general and sex steroid hormones in particular. Through feedback interaction with the hypothalamus and pituitary gland, sex steroid hormones are intimately involved in controlling such reproductively essential phenomena as the ovarian and menstrual cycles, ovulation, sperm development and acquisition of fertilizing ability, gamete transport, preparation of the uterus and subsequent implantation, embryo development, and parturition. Sex steroid hormones bind themselves to specific proteins called receptors in such target organs as ovaries, testes, and the uterus. The structure of these receptors especially for estrogens and progesterone is being investigated since interference with steroid-receptor interactions could potentially decrease fertility.

Gonadotropins are hormones secreted by the pituitary which act on the gonads (ovaries or testes) to make them produce their respective sex steroid hormones, the estrogens and androgens. Work continues on the types of receptors for gonadotropins during development of the gonads. Changing patterns of gonadotropin receptors in the testis reflect the development of its spermatogenic and hormonal elements. In the ovary, the growth of the cell which produces the ovum depends upon an increase in the cell wall of the number of receptors for gonadotropin. Interference with the number and type of receptors in the growing wall would cause cellular degeneration.

While preventing pregnancy through interfering with blastocyst implantation in the uterus has been a continuing goal of contraceptive development research, recent reports suggest that the blastocyst itself may be a promising site for fertility regulation. The blastocysts of some species appear to initiate implantation by emitting a signal. This unknown signal, believed to be a macromolecule, elicits a uterine response favorable for implantation. Evidence that the rabbit blastocyst secretes a gonadotropin-like material prior to implantation is compatible with macromolecular identity of such a signal. Whether the human preimplantation blastocyst secretes such a substance required for its own implantation is not yet known.

More progress has been made recently in understanding the processes involved in sperm production than in the past several decades. Sperm production is controlled by two male sex hormones, testosterone and follicle stimulating hormone (FSH). Testosterone stimulates sperm production, and FSH stimulates production of a protein (Androgen Binding Protein - ABP) to carry testosterone to those parts of the testis where sperm are produced. This new information suggests three possibilities for the development of male contraceptives: (1) A male contraceptive might prevent the transport of testosterone by ABP by blocking the binding of the hormone to the protein, (2) A male contraceptive might act by

blocking the secretion of FSH by the pituitary gland, or (3) A male contraceptive could prevent production of the ABP required for testosterone action.

Research on two inhibitors in ovarian follicles has provided significant new leads for contraceptive development. Small follicles appear to contain a substance which inhibits the formation of the corpus luteum (the ovarian structure which secretes progesterone). Egg development within the follicles appears to be blocked by a second inhibitor. If these inhibitors could be identified, they could be used to restrict fertility by blocking the progesterone required for pregnancy or by preventing maturation of the egg. These new findings offer especially promising approaches to fertility regulation because the inhibitors are naturally occurring substances which, therefore, might produce minimal undesirable side effects.

A final important new development in the fundamental biomedical research program is the extensive progress made in research on the luteinizing hormone releasing factor (LRF), a substance which indirectly causes ovulation by stimulating the release of another hormone (LH). Much of this research is aimed at the manufacture of LRF-like substances which will block the action of LRF in inducing ovulation or cause ovulation to occur predictably. Synthetic LRF-like substances may prove to be of great value in both regulation of fertility and alleviation of infertility. They may prevent ovulation by blocking the normal response of LH to LRF stimulation. They promise to improve the reliability of the rhythm method by fixing the time of ovulation, thereby defining a truly safe period.

3. Contraceptive Evaluation

To date the contraceptive evaluation program has focused on oral contraceptives and vasectomy. As a consequence of recent developments, a significant new initiative will be undertaken in the area of IUDs.

Long term surveillance of a large population of women has revealed an increase in average systolic and diastolic blood pressure and a six-fold increase in risk of hypertension among oral contraceptive users. Oral contraceptive use is also associated with a decrease in glucose tolerance, an increase in body weight, an increase in blood coagulability, and an increase in certain blood lipids. Continuing surveillance of this population is designed to identify to what extent such effects on known risk factors in cardiovascular disease can be used to identify subpopulations of oral contraceptive users likely to develop subsequent cardiovascular complications.

Studies also suggest a tendency among oral contraceptive users towards vitamin B6, folic acid, and zinc deficiency. Further investigations will attempt to ascertain the clinical significance of these deficiencies.

A series of new projects have been developed to pursue the relationships, if any, between various contraceptive methods currently in use and birth defects. The projects will evaluate oral contraceptives, the rhythm method, spermicidal agents, and IUDs. In addition to investigations of specific malformations suspected of being associated with oral contraceptives such as congenital heart disease and limb malformations, the studies will investigate other types of malformations.

Studies of the effects of oral contraceptives in various animal species will provide a basis for assessing the relative usefulness of each species as a research model for predicting effects in man.

Vasectomy

Studies to investigate possible adverse consequences of vasectomy are continuing. Two types of antibodies to sperm have been found in blood specimens from patients both before and after vasectomy. One type is present is half the patients before vasectomy, increases slightly two months after the operation, and subsequently shows little change. The other type is rare before vasectomy, increasing in incidence the longer the interval after the operation. These two types of antibodies are directed to antigens on different regions of the sperm surface. The possible medical significance of these antibodies will be investigated.

Studies are being conducted relating to the swollen sperm head antigen of human sperm identified during fiscal year 1974. Its chemical composition has been ascertained, and antibodies to it have been detected in 11 percent of 100 men vasectomized from one to four months and in 23 percent of men vasectomized for 12 months. Since the swollen sperm head antigen is of nuclear origin, the possibility of its cross reacting with nuclear material from non-reproductive tissues is being examined.

Several prospective clinical studies are investigating immune function before and after vasectomy. These studies have discovered circulating antibodies to sperm, some fluctuations in tests for cellular immune responses, and low levels of anti-nuclear antibodies in a small number of patients. Since these effects may be transient and unrelated to vasectomy, further studies are required. A prospective study of hormone levels in vasectomized men, initiated during fiscal year 1974, continues to reveal no adverse effects of vasectomy.

Program Development

During fiscal year 1975, a program will be developed to identify factors predictive of hypertensive response among oral contraceptive users and to evaluate the extent to which the hypertensive response is responsive to therapy after discontinuation of oral contraceptives.

Intrauterine devices are now used as a means of birth control by more than three million women in the United States. The efficacy,

frequency of minor complications, and expulsion rate of these devices have been well documented.

Serious complications and even a number of maternal deaths have recently been associated with IUDs. Available information suggests that severe complications are rare, but that the rate may vary for different devices. The infrequency of serious complications associated with IUDs would make a prospective investigation of this problem excessively costly and time consuming. Therefore, the NICHD will utilize a retrospective case-control research strategy to delineate the risk of specific severe complications, including maternal deaths, for all intrauterine devices currently in use and to identify subpopulations of women at high risk of such complications.

Because of the rarity of severe complications, even a case-control study will require the participation of approximately twenty major hospital centers in the country, using a common protocol and reporting information on cases and controls to a central coordinating unit.

During fiscal year 1975, the NICHD plans to initiate a study to determine the medical status of a large number of men vasectomized over the past several years. Such a study could rapidly provide an overall assessment of the possible medical consequences of the procedure. The NICHD also plans additional studies on purification of sperm antigens since purified antigens are required for improved methods of testing for cell-mediated responses to sperm.

B. Behavioral Sciences Research

The goals of the NICHD behavioral sciences program in population research are: (1) to ascertain the social, psychological, and economic determinants of fertility in the United States and (2) to assess the effects of population size, composition, and distribution.

1. Fertility in the United States

The National Fertility Survey of 1970 showed that white women married at 20 years of age or older tend to use more effective contraceptives than women married prior to age 20. This is not true of black women. Also an increasing proportion of women married during the 1960's used contraception prior to first pregnancy. Oral contraceptives were preferred over other methods by both Catholic and non-Catholic whites. However, the condom was the most frequently used first method among blacks. Another study indicated that couples who had used relatively effective contraceptive methods in early birth intervals showed lower average fertility. Several new studies are being initiated to ascertain the factors which influence the selection and utilization of contraceptive methods. According to the National Fertility Survey, during their first year of exposure to risk of pregnancy, twenty-six percent of

couples using contraception fail to delay a pregnancy they wish to postpone. Only 14 percent of such couples fail to prevent a birth they do not want at any time.

Investigators in Hawaii have conducted a study on the decision-making process regarding abortion. The study is based on survey data collected from over half of the women who conceived during a specific two month period in 1971 and who either carried their pregnancy to term, or who had a legal abortion. Women who had a stillbirth, a spontaneous abortion or an illegal abortion were not included. It was found that coitus was anticipated by the majority of women, but pregnancy was not planned for 58 percent of the women. Two-thirds of the women who did not want to become pregnant were not using a contraceptive method; yet, regardless of whether birth control was used or not, one of three women chose to have an abortion. The decision to have an abortion usually depended upon the woman's marital status, age, religion, and previous use of birth control. While no strong relationship seemed to exist between the types of contraceptive technique used and the decision to have an abortion, women who planned ahead to have an abortion if they became pregnant, were more often using contraception. This implies that for these women abortion was being used as a back-up method for failed contraception rather than a primary method of family planning.

Between 1970 and 1971, teenage illegitimacy dropped 10 percent in states with liberalized abortion policies but rose slightly (0.3 percent) in other states. White teenagers were the only group with rising legitimate birth rates between 1965 and 1970. However, in 1971 their marital fertility declined in states with liberalized abortion policies and continued to rise in other states.

A study of New York City women with recent first births indicated that a substantial proportion wishes that their first child had come later. Nearly 60 percent of the first births were unplanned, and more than a third were conceived out of wedlock. Inadequate knowledge of contraception and low motivation to avoid an unplanned pregnancy appear to be primary factors in pregnancies among women who are not seeking pregnancy.

The relationships between women's fertility and such factors as early labor-force participation, career aspirations, social and psychological pressures, and job status are being investigated. An analysis of 1970 Census data shows that education modifies the relationship between female employment and fertility. While approximately 23 percent of all white married women with a child under five worked in 1970, 34 percent of this group who had more than a college education worked. Other studies are exploring the extent to which this higher frequency of employment in spite of equal parity is the result of greater commitment to a career, greater ability to pay for childcare services, or other factors.

2. Trends in Fertility and Factors Contributing to Fertility Decline

Data from married women aged 18-39 indicate a continuing decline in the number of births to date as well as in the total number of children expected. Young women anticipated smaller completed families than did older women. Seventy percent of the young wives expected no more than two children, whereas only 40 percent of the older wives actually had families that small. One current study is examining the impact of women's norms concerning family size. In this study, women with no children or one child are perceived as less likable, less well-adjusted, and more selfish than the same women when presented as having two children. The strongest negative reaction is toward the women presented as having no children.

According to one investigator, variations in economic distress have played a significant part in the rise and fall of fertility since World War II. The findings support the hypothesis that the post-war baby boom arose from circumstances that produced a feeling of unusual affluence among young adults. In contrast, young adults who grew up during the prosperous conditions of the 1950's found it more difficult to achieve their higher material aspirations. This condition contributed to the continuing decline in fertility among young adults which began in the early 1960's. The investigator believes that oral contraceptives, liberalized abortion, and the women's liberation movement may have reinforced the impact of economic factors in inducing a decline in fertility. Four new studies will further explore the social and economic determinants of fertility trends in the United States between 1940 and 1970 -- the period of the baby boom and the subsequent fertility decline.

A study of the values associated with family size suggests that the anticipated rewards of children are most important in the decision to initiate family growth but that the recognition of the costs of children is most important in the decision to terminate family growth. The poor have more children and relative to means, pay more for them. Future studies will focus on the perceived economic, physical, psychological, and social costs of children for parents.

A long-term study of fertility in Taiwan shows two important changes: (1) a significant decline in desired number of children in all strata of the population, and (2) a large increase in contraceptive practice among young women, following a long period in which birth control was mainly adopted by older women. According to the results of a longitudinal study, Taiwanese women who desire no more children are successful in having no more.

3. Distribution of Population Growth and Migration

An analysis of migration trends in the U.S. during the 1960's

showed that blacks continued to migrate away from the South although the volume and rate of out-migration were lower than in the two previous decades. While the South and North historically experienced a net out-migration of whites and the West gained, this pattern no longer holds. The North continues to experience a net loss of whites through out-migration but the South is now gaining. There is no evidence of a substantial in-migration of northern-born blacks to the South nor does there appear to be a substantial return migration of southern-born blacks to the South. During the 1960's, the out-migration from rural areas and the concentration of both races within metropolitan areas continued.

4. Consequences of Population Growth

Data from a national sample of high school students indicate that even when socio-economic status is controlled, children from larger families tend to have lower measured intelligence quotients and lower academic skills. While parents accurately perceive many of the advantages of small families, there are still a number of misconceptions. The beliefs that there is a "middle child problem," that single children are spoiled, or that large families offer substantial advantages over small ones are not supported by the currently available research.

Small families appear to promote better physical care of the children. More physical, emotional, and financial resources are available to children in small families. Since social interaction between parents and children is greater in the small family, children may receive more interest, encouragement, and love. However, the increased social interaction can produce negative consequences if parents invest too much in the children and place too great a burden on them to live up to parental expectations. Such stresses may produce emotional disturbances in some children.

Since large families more frequently include unwanted children, researchers must control for the effects of unwantedness in investigating the effects of family size. In one study, children born to women who have been denied abortion demonstrated lower academic performance in all subjects in school than "wanted" children.

C. Institutional Development

1. Population Research Centers and Program Projects

In addition to project grants and contracts, NICHD supports population research conducted in Population Research Centers and Program Projects. Center Awards support facilities and services to improve the quality of ongoing programs. During fiscal years 1973 and 1974, Population Research Center Awards supported the following ten institutions for the studies noted: 1. Vanderbilt University - reproductive hormone actions and their molecular controls; 2. The University of Texas at Austin - population dynamics of minority groups; 3. Population Council at the Rockefeller University - fertility regulation and antecedents and consequences of fertility; 4. University of Wisconsin - demography and human ecology; 5. University of Chicago - reproductive biology and population genetics; 6. Harvard University - reproductive biology and human reproduction; 7. Johns Hopkins University - fertility in teenage women, family planning services, and fertility regulation; 8. Baylor Medical College - molecular biology of reproductive processes; 9. University of North Carolina - behavioral-social population problems; 10. Columbia University - research by the International Institute for the Study of Human Reproduction. Early in fiscal year 1975, Center Awards will be made to Princeton University for studies in demography and to the University of Pittsburgh for research in primate reproduction.

Program Project Grants are awarded to institutions for the support of multi-disciplinary research programs consisting of at least three interrelated projects. During fiscal year 1973, six Program Projects received support. During fiscal year 1974, eleven Program Projects were supported for the studies indicated: 1. Columbia University - reproductive endocrinology relevant to problems of human reproduction; 2. The University of Michigan - reproductive endocrinology from molecular to physiological levels; 3. The Northwestern University Medical School - molecular, cellular, and tissue mechanisms operative in the action of hormones upon target cells and tissues; 4. The Oregon Regional Primate Research Center - factors which control the events culminating in fertilization in nonhuman primates; 5. The University of Pennsylvania School of Medicine - biochemical, biological, and morphological events in the early processes of reproduction and development prior to implantation; 6. The University of Texas at Austin - control mechanisms at molecular to organismic levels; 7. Harvard University Medical School - reproductive biology, fertilization, embryogenesis; 8. Case Western Reserve - reproductive biology, events from ovulation to implantation; 9. University of Texas at Houston - male reproductive function; 10. University of California at San Diego - gametogenesis and reproductive biology; 11. Washington University - hormonal regulation of the reproductive tract.

2. Manpower Development

All NIH research fellowships are being phased-out. Therefore, no new applications (with the exception of applications for Research Career Development Awards) are being accepted.

A new Training Program authorized under Title I of the National Research Service Award Act of 1974 will provide for future NIH training activities. Regulations for this program are currently being prepared.

D. Coordination and Communication

The coordination of Federal population research programs and the communication of population research information is accomplished through the following activities:

Interagency Committee on Population Research

The Interagency Committee on Population Research (ICPR) coordinates the population research activities supported by Federal agencies and fosters the exchange of information among Federal population research programs. The Committee was established by the Secretary of HEW on October 5, 1970, and has been extended through June 30, 1976. The ICPR is chaired by the Director of NICHD's Center for Population Research and reports to the HEW Deputy Assistant Secretary for Population Affairs.

Inventory of Federal Population Research

An important product of the ICPR is the Inventory of Federal Population Research which has been updated annually since fiscal year 1969. It represents a cooperative effort on the part of the Federal agencies that fund population research projects. The Fiscal Year 1973 Inventory reports that Federal agencies supported about $54 million in population research during fiscal year 1973, approximately 11 percent less than the $61 million obligated in fiscal year 1972. An additional $23 million was invested in generating statistical data directly relevant to population research, a decrease of about $5 million from fiscal year 1972. This decrease was due to completion of much of the work on the 1970 Census. There was a slight decline in the total number of projects sponsored by Federal agencies, from 767 in fiscal year 1972 to 730 in fiscal year 1973. DHEW continued as the major Federal funding agency for population research, providing $44.1 million or 81 percent of the fiscal year 1973 total.

Analysis of Federal Population Research

The ICPR also prepared its Analysis of Federal Population Research -- Fiscal Year 1973. This annual report analyzes current Federally

supported population research and recommends research to meet information gaps in the population sciences.

Population Sciences: Index of Biomedical Research

Population Sciences: Index of Biomedical Research, a bibliographic journal published on a monthly basis, provides information concerning current biomedical research literature in the population sciences. Beginning with the September 1974 issue, the journal will be available only through a subscription placed with the Superintendent of Documents.

Population Research Monographs

The NICHD also disseminates population research information through publication of monographs. The monographs review and evaluate specialized areas of population research in the biomedical or social sciences and indicate the research required to obtain needed knowledge. Research monographs currently in press or final preparation include: The Walnut Creek Contraceptive Drug Study; Rural-Urban Migration Research in the United States; Handbook of Steroid Contraceptives; Fertility of the Yugoslav Population; and Population Psychology: Research and Educational Issues.

Publications of Workshops and Conferences

The publications resulting from NICHD conferences and workshops constitute a valuable addition to population research literature. Books added during fiscal year 1974 include: Biorhythms and Human Reproduction; Proceedings of a Research Conference on National Family Planning; and Oral Contraceptives and High Blood Pressure.

Mr. CONTE. Would you get us something for the record or this because this dovetails with the other committee?

Dr. KRETCHMER. All right.

Would you also like a detailed record on SIDS?

Mr. CONTE. I would appreciate it.

[The information follows:]

THE SUDDEN INFANT DEATH SYNDROME

In the United States, the sudden infant death syndrome (SIDS), also known as crib death, is the leading cause of death among infants between the first and twelfth months of life. It is estimated that each year approximately 7,500 to 10,000 infants, about two to three infants per 1,000 live births, succumb to this syndrome. Most victims are between the ages of one and six months. The incidence is highest between the second and fourth months of life.

The National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health has primary Federal responsibility for research on the sudden infant death syndrome. Other Federal programs related to SIDS involve the National Institute of Neurological Diseases and Stroke (NINDS) of the National Institutes of Health; the Bureau of Community Health Services, Office for Maternal and Child Health, Health Services Administration; the National Center for Health Statistics, Health Resources Administration; and the National Institute of Mental Health (NIMH), Alcohol, Drug Abuse, and Mental Health Administration.

Obligations for programs in Sudden Infant Death Syndrome

	1972	1973	1974	1975 estimated	1976 estimated
National Institutes of Health:					
National Institute of Child Health and Human Development	$3,550,000	$4,106,000	$5,300,000*	$4,700,000	$4,700,000
National Institute of Neurological Diseases and Stroke	---	105,000	---	---	---
Health Services Administration:					
Bureau of Community Health Services					
Maternal and Child Health	35,000	9,800	114,000	---	---
Health Resources Administration:					
National Center for Health Statistics	---	11,000	1,000	2,000	3,000
Alcohol, Drug Abuse and Mental Health Administration:					
National Institute of Mental Health	---	---	---	81,757	84,602
Total	$3,585,000	$4,231,800	$5,415,000*	$4,783,757	$4,787,602

*Includes restoration of 1973 impounded funds in the amount of $616,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

The sudden infant death syndrome strikes without warning. In the majority of cases the baby is apparently in good health and feeds without difficulty. While there may be evidence of a slight cold or stuffy nose, there is no serious upper respiratory infection present. The infant is placed in his crib for a nap or for the night and several hours later is found dead. Following autopsy, no cause of death can be identified. In a large proportion of the victims, however, minute hemorrhages have been found within the chest; the babies are otherwise free of abnormal tissue changes.

Crib death is a world-wide health problem. It occurs more frequently in males than in females. The incidence is higher in non-white than in white babies, in families of lower socioeconomic status, in premature infants, particularly those who had gestational ages between 34 and 35 weeks, and in babies who had recent infections. Twins may be especially vulnerable to SIDS. It is likely that this tendency is related to their typical lower birth weight or shortened gestational period. Most crib deaths in the United States occur in the cold weather months between November and March. The risk appears to be highest in crowded environments.

Why these babies die is unknown. Many reasons have been offered to explain the deaths, including neurophysiologic, immunologic, cardiorespiratory, endocrine, and infectious disease causes. There does not appear to be any single explanation. All factors believed to be associated with the syndrome appear to be intertwined. It is not known, however, which one of the associations is most important.

The Sudden Infant Death Syndrome Act of 1974

On April 22, 1974, President Nixon signed into law The Sudden Infant Death Act of 1974 (P.L. 93-270). The Act fixes by statute the responsibility of NICHD for the conduct of SIDS research; requires the Secretary to develop public information and professional educational materials; authorizes grants and contracts for projects to collect and analyze information as to the causes of SIDS and to provide information and counseling to families affected by SIDS; and requires specific reports to Congress pertaining to progress of programs concerned with SIDS.

The National Institute of Child Health and Human Development has been designated as the lead agency for P.L. 93-270 and has been given responsibility for coordination and development of an implementation plan of the law. The implementation plan was submitted to the Assistant Secretary for Health on September 1, 1974. It has also been incorporated into the DHEW Child Health Task Force Operational Plan for FY 1975. In addition, the National Institutes of Health selected SIDS for FY 75 tracking through the NIH Operational Planning System.

The DHEW has established an interdepartment committee to coordinate Federal efforts in SIDS. It is chaired by an office of the NICHD and has representation from the National Institute of Neurological Diseases and Stroke; the National Institute of Mental Health; Office for Maternal and Child Health, Bureau of Community Health Services; the National Center for Health Statistics, and the Office of Program Implementation, Office of the Assistant Secretary for Health. Representation from other related and interested Federal programs will be included as appropriate.

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A meeting to discuss approaches to implementation of the SIDS Act was held at the National Institutes of Health on August 5, 1974, under the auspices of the Interagency Panel. Its specific purpose was to obtain input from the scientific community, SIDS parent organizations, and other concerned citizens. Those attending included (a) officers and other members of parent organizations, (b) physicians, including forensic pathologists (medical examiners), psychiatrists (psychological counsellors), and pediatricians, (c) biostatisticians and (d) communications specialists.

Research Objectives in SIDS

During 1974 the NICHD continued to expand its research efforts on the sudden infant death syndrome. The objectives were:

1. To increase understanding of underlying mechanisms of the syndrome.

2. To identify infants at risk of becoming victims and to explore preventive approaches.

3. To elucidate the impact of a sudden and unexpected infant death on the subsequent behavior of parents and siblings.

4. To learn more about the management of SIDS cases in the United States and to develop guidelines for coroners, medical examiners, and pathologists in handling these cases.

5. To inform the scientific and general communities about SIDS through workshops, conferences, and publications.

NICHD Workshop and Lecture Series

Since 1971, the NICHD has been sponsoring a series of research planning workshops on this problem, to identify specific research areas in need of in-depth study. These workshops bring together expert investigators and attract a number of scientists to work on the problem of SIDS. A summary report of each Workshop has been published or is currently in press.

In February 1974, the NICHD initiated a lecture series on New Research Perspectives in the Sudden Infant Death Syndrome. The purpose of these lectures is to highlight recent research findings and share them with the scientific community and public. Four presentations were made in 1974. The subjects of the lectures were: New Approaches in Evaluating Infants at Risk; Hypoventilation: A Possible Cause for SIDS; Sleep Disorders and SIDS; and Infectious Disease Aspects of SIDS.

NICHD Research Program

The NICHD has developed its SIDS research around seven emphasis areas:

1. Abnormal sleep patterns related to breathing, circulation and other functions essential to life.

2. Respiratory, cardiac, and circulatory responses to such stimuli as excess carbon dioxide in the blood or oxygen deficiency.

3. The body's system for metabolic and temperature regulation and its response to environmental conditions.

4. The baby's developing immune system and how defects in development may predispose an infant to the syndrome.

5. The distribution of the sudden infant death syndrome within the population and characteristics surrounding its occurrence in order to identify infants at high risk.

6. Studies of the structural and functional changes in tissues and organs.

7. The psychological stresses experienced by the family and the community when a sudden and unexplained infant death occurs.

In FY 1974 there were 109 ongoing research projects pertaining to SIDS. They included 27 grants and contracts for research specifically concerned with SIDS, and 82 others for grants and contracts for related studies. FY 1974 support approximated $5.3 million compared with $4.1 million in FY 1973. Funding for FY 1975 will approximate $4.7 million.

There have been several important new findings about SIDS during the last fiscal year. It has been shown in infants that periodic cessation of breathing (apnea) during sleep and associated changes in heart rate are part of a developmental pattern that occurs during the early months of life. It has also been observed that the frequency and duration of apneic episodes in infants during sleep is influenced by the same factors that have been shown to characterize the infant at high risk for SIDS--low birth weight, shortened gestation, mild upper respiratory infection. Studies in kittens have revealed that they have periods of apnea during sleep, and when they are deprived of sleep, frequency of apneic episodes in a subsequent sleep period is markedly increased. Continuous periodic cessation of breathing, such as that which occurs during sleep apnea, can affect availability of oxygen to tissues. One of our grantees has shown that in some infants who have died from SIDS, the thickness of the muscle mass surrounding the small pulmonary arteries indicates that there has been a deficiency in the amount of oxygen entering the air spaces of the lung. This observation is indicative of a persistent chronic lack of oxygen to the area; this oxygen lack may be the result of prolonged periods of apnea during sleep.

NICHD Information Program

The Institute has several publications available for distribution to the scientific community and general public. Publications in print include:

Summary of Proceedings: Second International Conference on Sudden Infant Death Syndrome, Seattle, 1969

Facts About The Sudden Infant Death Syndrome

SIDS: Selected Annotated Bibliography, 1960-1971

National Library of Medicine Literature Search on Reaction to Infant Death by Family and Social and Legal Institutions

Research Planning Workshop on The Sudden Infant Death Syndrome

SIDS Research Planning Workshop: Behavioral Considerations

SIDS Research Planning Workshop: Developmental Aspects of Infection and Immunology

SIDS Research Planning Workshop: Cardiorespiratory Phenomena

SIDS Research Planning Workshop: Neurophysiological Factors

SIDS Research Planning Workshop: Epidemiology

SIDS Research Planning Workshop: Pathology

Publications which should be available for distribution in FY 1975 include:

SIDS: Information for Parents and Rescue Workers

SIDS: Management of Cases in the United States

SIDS: Hope For Tomorrow's Children

SIDS Research Planning Workshop: Identifying Infants at Risk

SIDS Research Planning Workshop: Development of the Upper Airway

SIDS Research Planning Workshop: Post Mortem Evaluation for Investigative Efforts

SIDS Research Planning Workshop: Approaches to Establishing Case Registers and Clinical Trials

SIDS: Selected Annotated Bibliography, 1972-1974

The Sudden Infant Death Syndrome Act of 1974: Approaches to Implementation

The Role of Cardio-Respiratory Electronic Monitoring of Young Infants in the Home Environment

NATIONAL INSTITUTES OF HEALTH

The National Institute of Neurological Diseases and Stroke

The National Institute of Neurological Diseases and Stroke (NINDS) has contracted with the Pennsylvania State University to analyze the sudden infant death syndrome (SIDS) cases that occurred in the Collaborative Perinatal Project (CPP). All deaths among the 50,000 children of the CPP have been verified and classified; 115 SIDS cases have been identified. A set of matched controls from the CPP population has been selected. A multivariate analysis of 30 pregnancy and neonatal variables is under way in an effort to identify characteristics associated with SIDS occurrence. One of the important features of the CPP data as it pertains to SIDS cases, is that the information was collected prospectively, that is, these data were collected prior to the death. Biases inherent in retrospectively-collected data were thus avoided.

HEALTH SERVICES ADMINISTRATION

Bureau of Community Health Services, Office for Maternal and Child Health

Sudden infant death syndrome (SIDS) activities in the Bureau of Community Health Services, Office for Maternal and Child Health, were intensified considerably in 1974. The emphasis has been to develop the implementation plan for the service, professional education, and public information portions of the Sudden Infant Death Syndrome Act of 1974. Preparation of regulations required for the solicitation of grant application and contract proposals is in progress.

In September 1974, an ad hoc advisory committee was convened to consider the issues related to the service portions of the legislation. The members of this committee represented medicine, nursing, social work, medical examiners and coroners, and all are actively engaged in the delivery of counseling and other follow-up services to families who have experienced a loss of an infant to SIDS. This conference focused on the characteristic components necessary for service programs responsive to the needs of families as well as to the legislative mandate. The recommendations of this group will be incorporated into the SIDS program guidelines where appropriate.

A contract was awarded to script and produce a 20-minute, 16 mm color, sound training film for health professionals on Sudden Infant Death Syndrome. The purpose of the film is to increase the awareness of health professional audiences about the trauma and suffering experienced by families who have lost an infant to SIDS. It also will serve to motivate the health professionals to provide counseling to the families affected by SIDS. It is anticipated that the film will be completed by February 1975.

A teaching guide is being prepared to accompany the film. It will provide the discussion leader with some workable suggestions for helping parents. In addition it will include factual knowledge about the syndrome itself.

A one-year study designed to determine causes of death in all infants aged 28 days to 1 year in New York City and to make decisions with regard to the degree of preventability of death is currently funded by Maternal and Child Health. The sudden infant death syndrome is one category of deaths which is being investigated. Numerous cooperative arrangements with health care and social welfare agencies have been made in order to accurately determine the causes of death and the possible effects on postneonatal mortality of families' social and physical environments as well as their relationships to health care systems. This study will be completed early in 1975.

In several large cities and in some States, studies have been made in developing coordinated community service programs. Oregon is a notable example of a statewide approach to the problems of SIDS. The key to this voluntary program is an effective referral system coordinated at the State level between the medical examiner and the public health department. Either voluntarily or as States pass legislation related to the sudden infant death syndrome, similar statewide plans are evolving, as for example in California. Numerous cities and counties also are initiating voluntary service programs responsive to the family concerns.

Generally, through Maternal and Child Health activities of the local or State health departments, information about the sudden infant death syndrome and counseling is becoming more available to families. Services have been initiated with limited local resources in cities such as Seattle, New York, Los Angeles, Chicago and Philadelphia.

During this past year SIDS and its related concerns have received increased visibility through presentation of informational and educational programs resulting from MCH activities at national meetings, such as APHA; Maternal and Child Health national and regional staff conferences; local health department inservice programs, such as in Cleveland, Ohio; and at State nursing association meetings, for example, in Alabama.

HEALTH RESOURCES ADMINISTRATION

National Center for Health Statistics

During FY 74 a new coding scheme for sudden death was developed. It went into effect in calendar year 1973. Work was also begun on an article nosology; guidelines explained this new coding change to coders, pointing out to registrars that the term "sudden death" was an acceptable one, and they should discontinue querying it.

ALCOHOL, DRUG ABUSE AND MENTAL HEALTH ADMINISTRATION

National Institute of Mental Health

In June 1974, the National Institute of Mental Health (NIMH) entered into a contract with the National Foundation for Sudden Infant Death, Inc., to develop and maintain a two-year program designed to provide educational and counseling information and service to medical professionals, paraprofessionals and families which have cases of sudden infant death.

Specifically, the contractor will identify and visit health departments in major American communities throughout the nation in order to consult with health officers and public health nursing directors on the humanizing of medical treatment for SIDS cases. Through the use of existing medical knowledge and expertise, publications, and health resources, the contractor will provide recommendations for procedures and guidelines in establishing a program to handle SIDS cases in a more compassionate and sensitive manner. Health consultants, staffs of community mental health centers, and representatives of parents organizations will be identified and their involvement encouraged in the communities visited.

The Division of Special Mental Health Programs, NIMH, conducted a special, two-day invitational work conference on the mental health/behavioral aspects of SIDS on November 20-21, 1974. The purpose of this meeting was for NIMH staff to explore with consulting experts, program content and strategies in connection with NIMH's responsibilities in implementing the Sudden Infant Death Syndrome Act of 1974. Eight consultants representing various mental health and behavioral science disciplines as well as medicine, nursing, and the clergy developed guidelines for specific research, training, and demonstration activities concerned with the mental health/behavioral aspects of SIDS.

DISSEMINATION OF INFORMATION

Mr. CONTE. Would you outline, and you can do this for the record, the actions which you are taking to disseminate your research findings to the health care delivery system.

Dr. KRETCHMER. We certainly will give a report for the record. I might say we are trying to develop new techniques for dissemination of information. Having come from outside of the Federal Government, I feel very deeply about this.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

DISSEMINATION OF INFORMATION

Information dissemination is of utmost significance to the National Institute of Child Health and Human Development. It is only through sharing of information that advances made in biomedical research can reach their logical end, the health care delivery system. The Institute will continue to disseminate these research findings not only to the scientific community, the physician, and other health care personnel, but as importantly to the general public as well. The media used include: scientific publications, general publications, the press, radio and television, meetings and conferences, and integrated information campaigns. In conjunction with the Bicentennial activities of the Nation, the National Institutes of Health is involved by sponsoring an open house for the public and various exhibits both at the National Institutes of Health and other locations in the Washington, D.C., area.

A recent example of the Institute's information dissemination endeavors, which is considered to have achieved success, is the Down's syndrome (mongolism) education campaign. Through varied media, pertinent health care information reached many segments of the population, including physicians and most importantly, women at high risk for producing offspring with Down's syndrome. Similarly, the information campaign on the sudden infant death syndrome has reached all segments of the community, medical, scientific, and lay.

TRAINING

Mr. CONTE. What is the manpower situation in your field of research? Are you going to be adversely affected by the changes in the training grant program?

Dr. KRETCHMER. Most of our training will be in the area of postdoctoral fellowships. There really will not be any major adverse effect. We have 263 fellowships in fiscal 1975. We estimate that we will be able to support 235 fellowships in fiscal 1976.

PERINATAL BIOLOGY CENTER

Mr. CONTE. Can you tell us what the progress has been in new facility and the NIH clinical center to study pregnancy, infant mortality and mobidity?

Dr. KRETCHMER. The perinatal biology center started operating early in 1975. It consists of a total of 15,000 square feet and occupies three additional floors on a wing of the Clinical Center. Floor 8 has now been moved into and is a research laboratory floor. On floor 9, we have developed facilities for six patients. Still under construction is floor 10, which comprises the delivery rooms and the nurseries. However, we probably won't be able to open it.

Mr. CONTE. Floor 10?

Dr. KRETCHMER. Floor 10.
Mr. CONTE. Because of budgetary constraints?
Dr. KRETCHMER. Because of budgetary and position constraints

MULTIYEAR FUNDING

Mr. CONTE. Could you tell us what programs of the Institute will require multiyear funding in this budget and how much these programs will involve?

Dr. KRETCHMER. Multiyear funding in 1975 involves about $3 million, mostly in the area of population contracts. We estimate very little multiyear funding in 1976.

NUTRITION

Mr. CONTE. Will you outline the status of studies concerning nutrition of expectant mothers during pregnancy?

Dr. KRETCHMER. The question of nutrition of pregnant mothers is an area that I am particularly concerned with. We have a number of studies in process. We are particularly concerned, for example, with the relationship of nutrition to the toxemia of pregnancy, when the mothers develop high blood pressure and have protein in the urine. They are considered high risk mothers and their babies are invariably high risk babies.

We have had a continuing project in Guatemala and another in Harlem. We have a number of projects dealing with animal models, ranging from rats to monkeys, throughout the country. This is an area where we are in fact, putting a good deal of effort. I am wondering if I can find a number to give you.

Mr. CONTE. You can put that in the record.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

FUNDING OF RESEARCH ON NUTRITION IN PREGNANT WOMEN

The funding of research on nutrition in pregnant women for 1975 is $3,339,000, compared to $3,266,000 in 1974. This compares to $11,902,000 and $11,798,000 respectively for the Institute's total nutrition research effort.

PARENTAL FACTORS

Mr. CONTE. Do you have any preliminary results in your study in the way fathers interact with their young children?

Dr. KRETCHMER. Many of the activities of the Center for Population Research have to do with studying families, in other words, parents relative to children. In addition, although we call our new center the Center for Research for Mothers and Children, we are concerned with parental interaction with infants.

We have studies throughout the country in the particular area which has to do with the relationship between parents and infants. We use as our study group the premature infant because the premature infant brings about in many fathers intense reactions. In contrast to the situation until about 1962 where parents were never allowed into

those nurseries, people now freely go into the nurseries, and no longer with masks and caps.

Mr. CONTE. A lot of fathers witness the birth.

Dr. KRETCHMER. A lot of fathers are in the delivery room and observe the mothers and babies. So our nurseries, rather than being closed, are open.

Consequently, the family is available for study and the interactions between mother, father, and infant are available. Another reason why premature infants are utilized is because they are in the hospital 30 or 40 days so the environment is controlled. Plugged into those studies are home visits to learn what is happening in the home. That was a long answer. I could have summarized it by saying, "Yes."

ZINC DEFICIENCY

Mr. CONTE. You say another finding is that zinc deficiency causes pica, which makes a child eat unnatural foods. Is that the child who eats dirt?

Dr. KRETCHMER. Yes; in the area I come from, New York City, the children used to eat plaster off the walls. The children would go into the park and eat dirt. That is called pica. Zinc deficiency is not the only cause, but there is an eating of abnormal things shown in children who do have zinc deficiency. Some of these children also have psychological problems.

Mr. CONTE. You mean most of the children who are afflicted with lead poisoning from paint are afflicted with pica also?

Dr. KRETCHMER. Exactly; lead poisoning from paint happens particularly in older dwellings where lead paint was used. We are studying part of the problem, the mechanism. The FDA is of course involved in that. If I am correct, lead paint is not permitted to be used in dwellings anymore.

Mr. CONTE. Not any longer, but there are a lot of old dwellings that have it and we still have cases of it. This committee appropriates quite a bit of money for lead-poisoning campaigns.

Dr. KRETCHMER. Those children would also eat the plaster off the walls in a house. So they would eat the plaster and also get lead poisoning.

Mr. CONTE. For the record, will you tell us what zinc deficiency is?

Dr. KRETCHMER. Yes.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

EXPLANATION OF ZINC DEFICIENCY

Zinc deficiency in humans is manifested by growth failure, delayed sexual maturation, impaired taste sensation and extremely slow healing of wounds. Although only a small number of U.S. children with these symptoms have been studied as yet, it appears that low concentrations of zinc in the hair may be a valid index of the individual's status for this nutrient. The diet in many homes in this country, regardless of socioeconomic status, may be marginal or somewhat inadequate in zinc content. The upper middle class children studied were classified as "picky eaters" by their mothers. Review of their diets showed that they selected foods low in zinc. For example, their main source of animal protein was milk, a poor source of zinc, and they ate very little meat although it

was readily available. Investigators studying zinc-deficient individuals in other countries report that they frequently eat dirt, a situation sometimes called pica.

ABORTION

Mr. CONTE. The thing that bothers me, as I sit on this committee and I hear such an intelligent man as you with such great programs which really move me and stimulate me, I just keep coming back to the abortion issue which troubles me greatly. I don't know the answer. I wish somebody could tell me. Here we are spending over $100 million in this field and trying to save children. Yet at the same time there is a segment of society that wants to destroy children. I wish sometime we could sit down and discuss this thing.

Dr. KRETCHMER. I would be delighted, Mr. Conte.

Mr. FLOOD. My colleague, Mr. Shriver, has asked me to furnish the following questions and have you respond to them for the record.

Dr. KRETCHMER. I would be glad to do so.

[The questions and answers follow:]

MENTAL RETARDATION

Question. Dr. Kretchmer, you mentioned the reorganization you have undertaken at the Institute. Would you describe how this reorganization affects ongoing mental retardation programs and centers?

Answer. The reorganization of the Institute reflects primarily the focusing of the Institute's child health programs as research for mothers and children. Since the mental retardation program is an important part of this research effort for mothers and children, the effect is better integration with the other research programs of the Institute. This reorganization will not affect the funding or administration of the mental retardation programs or centers.

Question. Is it your intent ot maintain a high priority for mental retardation centers? How does your budget reflect this?

Answer. It is definitely our intent to maintain a high priority for mental retardation centers program, the focus for a major portion of our mental retardation research, and an invaluable multi-disciplinary resource. This commitment is reflected in the budget' in these times of budget cutting and belt-tightening, we have kept the line item of core support for the Centers at the same level as in the past. In addition, the percent of mental retardation monies being spent in Center-related research will remain approximately the same in 1976.

Mr. FLOOD. That concludes this hearing. Thank you very much.

Dr. KRETCHMER. Thank you, Mr. Chairman.

Justification of the Budget Estimates

Appropriation Estimate

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

To carry out, except as otherwise provided, title IV, parts E and I, of the Public Health Service Act with respect to child health and human development, [$141,966,000] *$106,062,000.*

For "National Institute of Child Health and Human Development" for the period July 1, 1976, through September 30, 1976, $24,449,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Amounts Available for Obligation[1/]

	1975 Estimate[2/]	1976 Estimate
Appropriation	$141,966,000	$106,062,000
Comparative transfers to:		
"Office of the Director, NIH" (Transfer of the Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	-40,000	---
"Office of the Director, NIH" (Transfer of funds for public affairs reorganization)	-25,000	---
"Research Resources" (For the funding of the Rhesus Monkey Supply Program)	-112,000	---
"National Institute on Aging" (Transfer of aging activities in accordance with the Research on Aging Act of 1974)	-13,722,000	---
Total, obligations	126,067,000	106,062,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 - $61,000; 1976 - $45,000.

2/ Excludes 1973 restoration in the amount of $39,000.

Summary of Changes

1975 Estimated obligations	$126,087,000
1976 Estimated obligations	106,062,000
Net change	-20,005,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1975 pay, FICA, and health benefits increases	--	---	--	+$173,000
2. Within-grade pay increases	--	---	--	+139,000
3. Wage Board pay increases	--	---	--	+2,000
4. One extra day of pay	--	---	--	+26,000
5. Bureau of Employee Compensation	--	---	--	+3,000
6. Increased cost of postage	--	---	--	+7,000
7. Increased service and supply fund costs	--	---	--	+57,000
8. Federal Telecommunications System	--	---	--	+9,000
9. Payment to "National Institutes of Health Management Fund"	--	---	--	+1,246,000
Subtotal	--	---	--	+1,662,000
B. Program:				
1. Research grants:				
a. Noncompeting continuations	--	$41,848,000	--	+32,589,000
b. Competing (new, continuations, and supplementals)	--	29,003,000	--	+7,957,000
c. Special programs	--	7,633,000	--	+28,000
Subtotal	--	---	--	+40,574,000
Total, increases	--	---	--	+42,236,000

Summary of Changes - Continued

	1975 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Decreases:				
A. Program:				
1. Research grants:				
a. Noncompeting completed, converted to competing status, or terminated.....	--	41,848,000	--	-32,038,000
b. Competing completed or converted to noncompeting.	--	29,003,000	--	-29,003,000
2. Fellowships: Noncompeting completed.....	--	3,639,000	--	-218,000
3. Training grants: Noncompeting completed.....	--	6,218,000	--	-124,000
4. Research contracts.....	--	19,043,000	--	-858,000
5. Positions.....	358	---	-9	---
Total, decreases	--	---	-9	-62,241,000
Total, net change	--	---	-9	-20,005,000

Explanation of Changes

Increases:

A. Built-in: These increases will provide: $173,000 ($123,000 in Intramural, laboratory and clinical research and $50,000 in Research management and program services) for the annualization of 1975 pay, FICA, and health benefits increases; $139,000 ($83,000 in Intramural, laboratory and clinical research and $56,000 in Research management and program services) for within-grade pay increases in 1976; $2,000 for wage board pay increases in Intramural, laboratory and clinical research; $26,000 ($12,000 in Intramural, laboratory and clinical research and $14,000 in Research management and program services) for one extra day of pay in 1976; $3,000 in Research management and program services for Bureau of Employee Compensation increased costs; $7,000 in Research management and program services for increased costs in postage; $57,000 for increased rates in the service and supply fund for Intramural, laboratory and clinical research; $9,000 in Research management and program services for the increased costs associated with the Federal Telecommunications System; and $1,246,000 for increased payment to the NIH Management Fund for centrally furnished services (+$1,337,000 in Intramural, laboratory and clinical research and -$91,000 in Research management and program services).

Explanation of Changes - Continued

B. Program:

1. Research grants:

a. The increase of $32,589,000 in noncompeting regular research grants represents the increased cost for continuation of previously awarded grants plus "new" continuation awards.

b. The amount of $7,957,000 in competing regular research grants reflects the funding of high priority competing awards in 1976.

c. The increase of $28,000 in special programs provides for the increased costs of scientific evaluation grants.

Decreases:

A. Program:

1. Research grants:

a. The decrease of $32,038,000 reflects $12,554,000 in noncompeting regular research grants that were completed in 1975 or that are being converted to competing status in 1976; and $19,484,000 in grants that are being terminated.

b. The decrease of $29,003,000 reflects the completion or conversion to a noncompeting status of competing grants awarded in 1975.

2. The decrease of $218,000 in noncompeting fellowships represents 28 noncompeting awards which were completed in 1975.

3. The decrease of $124,000 in noncompeting training grants reflects the phase-out of this program after the training under previously approved training grants is completed.

4. The decrease of $858,000 in research and development contracts reflects a reduction in the number of child health and population contracts that will be awarded, particularly in the areas of mental retardation and contraceptive development.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
63	Population.....	---	$ 45,039,000	---	$ 36,123,000	---	-$ 8,916,000
70	Child health.....	---	62,345,000	---	49,594,000	---	- 12,751,000
84	Intramural, laboratory and clinical research.....	188	11,413,000	182	13,027,000	- 6	+ 1,614,000
88	Research management and program services.....	170	7,270,000	167	7,318,000	- 3	+ 48,000
Total obligations.....		358	126,067,000	349	106,062,000	- 9	- 20,005,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	358	349	- 9
Full-time equivalent of all other positions	85	85	--
Average number of all employees	429	429	--
Personnel compensation:			
Permanent potitions	$ 6,869,000	$ 7,111,000	+$ 242,000
Positions other than permanent	744,000	769,000	+ 25,000
Other personnel compensation	147,000	154,000	+ 7,000
Subtotal, personnel compensation	7,760,000	8,034,000	+ 274,000
Personnel benefits	1,171,000	1,240,000	+ 69,000
Travel and transportation of persons	293,000	276,000	- 17,000
Transportation of things	45,000	45,000	---
Rent, communications, and utilities	300,000	320,000	+ 20,000
Printing and reproduction	205,000	200,000	- 5,000
Other services:			
Project contracts	19,043,000	18,185,000	- 858,000
Payment to NIH management fund	4,348,000	5,594,000	+ 1,246,000
Other	2,806,000	2,896,000	+ 90,000
Supplies and materials	1,155,000	1,250,000	+ 95,000
Equipment	600,000	490,000	- 110,000
Grants, subsidies, and contributions	88,341,000	67,532,000	- 20,809,000
Total obligations by object	126,067,000	106,062,000	- 20,005,000

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Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1975 House Report	
1. The Committee was concerned that not enough research has been done in aging (pages 39 and 40).	1. In accordance with the Research on Aging Act of 1974, the Institute's research activities in aging will be transferred to the National Institute on Aging.
1975 Senate Report	
1. The Committee was appalled with this nation's high infant mortality rate (page 59).	1. The Institute has expanded its efforts to reduce infant mortality and morbidity.
2. The Committee was concerned that information regarding the Institute's accomplishments was not being broadly disseminated (page 59).	2. The Institute concurs with the concern and efforts are underway to develop better means to disseminate research results to physicians, research scientists, and the lay public.
3. The Committee directed that within the funds appropriated by Congress, NICHD allocate up to $16,000,000 for approved and meritorious program projects and research programs in the Mental Retardation Research Centers (page 60).	3. Within the 1975 operating level, the Institute plans to spend approximately $14,500,000 at the Centers.
4. The Committee directed the Institute to give the highest priority to those research areas which encompass all of the child health activities (page 60).	4. The Institute is implementing this directive by establishing a Center for Research for Mothers and Children which will provide closer coordination and increased emphasis to the child health research efforts. The interrelated factors at points in the life span which predispose events at later points in life are being given the highest priority.

5. The Committee recommended that all aspects of the population research program be emphasized (pages 60 and 61).	5. The Institute is continuing to emphasize the population research program. In 1975, funding for this activity will be $50,648,000.
6. The Committee expressed concern that aging research was not receiving adequate attention (page 61).	6. In accordance with the Research on Aging Act of 1974, the Institute's research activities in aging will be transferred to the National Institute on Aging.
7. The Committee instructed that a portion of the Congressional increase as well as the necessary positions be made available for the Institute's new perinatal biology facility located in the NIH Clinical Center (page 61).	7. In 1975, the construction of the new perinatal biology facility was completed. This intramural research program will be continued in 1976.

Authorizing Legislation

Legislation	1976 Authorization	1976 Appropriation Requested
Public Health Service Act Section 301 - Research and Investigation, in general	Indefinite	
Title IV, Part E - National Institute of Child Health and Human Development	Indefinite	$96,547,000 2/
Title IV, Part I - National Research Service Awards	1/	9,515,000 2/

1/ Authorization expires June 30, 1975; extension legislation is proposed.

2/ Funding estimate only.

National Institute of Child Health and Human Development

COMPARABLE

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$ 50,017,000	$ 50,017,000	$ 51,175,000	$ 51,524,000
1967	57,294,000	57,494,000	60,994,000	60,994,000
1968	64,105,000	64,105,000	69,175,000	64,092,000
1969	71,191,000	66,656,000	72,156,000	68,923,500
1970	71,649,000	68,895,000	76,597,000	72,989,000
1971	89,723,000	89,856,000	89,856,000	90,180,000
1972	99,636,000	105,567,000	121,532,000	112,326,000
1973	110,031,000	125,881,000	155,452,000	125,881,000 A/
1974	106,611,000	125,186,000	135,186,000	125,387,000 B/
1975	110,092,000	105,133,000 D/	128,271,000	126,067,000
1976	106,062,000			

NOTES: A/ This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

B/ Appropriation after reduction.

C/ The years 1966 through 1974 include funds for aging research, since the change in the budget structure from mechanism to program did not take place until 1975.

D/ Excludes research and development contracts which were not considered by the House due to lacking authorization.

National Institute of Child Health and Human Development

ACTUAL

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$ 53,524,000	$ 53,524,000	$ 55,024,000	$ 55,024,000
1967	61,448,000	61,422,000	64,922,000	64,922,000
1968	68,621,000	68,621,000	74,621,000	68,621,000
1969	75,394,000	70,859,000	76,359,000	73,126,500
1970	75,852,000	73,098,000	80,800,000	77,192,000
1971	93,303,000	94,436,000	94,436,000	94,760,000
1972	103,232,000	109,668,000	126,093,000	116,427,000
1973	127,244,000	130,429,000	160,000,000	130,429,000 A/
1974	106,679,000	125,254,000	135,254,000	125,455,000 B/
1975	124,897,000	120,232,000 C/	145,000,000	141,966,000
1976	106,062,000			

NOTES: A/ This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

B/ Appropriation after reduction.

C/ Excludes research and development contracts which were not considered by the House due to lacking authorization.

Justification

National Institute of Child Health and Human Development

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	358	$ 8,931,000	349	$ 9,274,000	- 9	+$ 343,000
Other expenses	---	117,136,000	---	96,788,000	---	- 20,348,000
Total	358	126,067,000	349	106,062,000	- 9	- 20,005,000

General Statement

The mission of the National Institute of Child Health and Human Development is to contribute to the good health of all citizens through efforts to understand the many factors, both biological and behavioral, related to the adaptation of the world's population to available resources and the expansion of knowledge on family planning, child health, maternal health and human development.

Following enactment of the Research on Aging Act of 1974, study of the aging period of the life span has shifted to the purview of the National Institute on Aging, for which a separate appropriation is requested in 1976. The Institute maintains its responsibilities and concerns for: research for mothers and children; research regarding human development; and research in population and reproductive phenomena.

A number of agencies within the Department of Health, Education, and Welfare, concentrate on programs, some of which include biomedical and behavioral research, directed toward family planning and improved health for mothers and children. The Institute is the focal point and major research arm for these scientific endeavors. The goals of the Institute are accomplished through research to assure a pregnancy and subsequent infancy of maximum health, as well as to provide conditions for optimum development of the child so that full physical and mental potential can be attained by the adult. These objectives are interdependent with a broad understanding of family structure, the dynamics of human population, and the reasonable regulation of its growth. Thus, the Institute has an interest in all problems affecting human development.

To accomplish its goals in the area of population and reproduction research, the Center for Population Research (CPR) was established, which has responsibility for understanding the forces affecting population growth, the development of contraceptive methods, and discovering the factors that determine acceptability of contraceptive methods and how these influence fertility patterns. In addition, the focus of the intramural research effort in population is the development of scientific data and theory basic to reproductive biology.

A Center for Research for Mothers and Children (CRMC), has been developed to advance knowledge on pregnancy, infancy and childhood as well as to examine the problems of human development from both a psychosocial and a biological standpoint, with special reference to the causes and amelioration of the problems of the mentally retarded. The CRMC, together with the intramural program for maternal and child health research, has the responsibility for understanding all factors related to the unmet health needs of mothers and children and will be concerned with health problems occuring in the earliest stages through adulthood.

In summary, the National Institute of Child Health and Human Development fosters good health and well-being throughout the life span through studies of the factors affecting population and promotes the best possible outcome of pregnancy by a focus on research for mothers and children. The Institute will influence the direction of research, and ultimately national health policy, to assure that the health needs of children are met in order to develop the healthiest possible adult population for this nation.

DHEW - National Institutes of Health

CROSSWALK - 1975 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute of Child Health and Human Development
(in thousands)

Program \ Mechanism	Research Grants									
	Regular Program		Specials		Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Non-competing	Competing	Multi disciplinary Centers	Other	Grants	Fellowships				
1. Population.....	$14,025	$11,961		$ 715	$2,232	$1,313		$14,793		$ 45,039
2. Child health.....	27,823	17,042	$5,608	1,310	3,986	2,326		4,250		62,345
3. Intramural, laboratory and clinical research....							$10,715		$ 698	11,413
4. Research management and program services.....									7,270	7,270
Total obligations.....	41,848	29,003	5,608	2,025	6,218	3,639	10,715	19,043	7,968	126,067

Excludes 1973 appropriation restorations.

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute of Child Health and Human Development
(in thousands)

Program \ Mechanism	Research Grants				Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials							
	Non-competing	Competing	Multi disciplinary Centers	Other	Grants	Fellowships				
1. Population.....	$16,062	$1,936		$ 725	$2,187	$1,209		$14,004		$ 36,123
2. Child health.....	26,337	6,021	$5,608	1,328	3,907	2,212		4,181		49,594
3. Intramural, laboratory and clinical research....							$12,301		$ 726	13,027
4. Research management and program services.....									7,318	7,318
Total obligations.....	42,399	7,957	5,608	2,053	6,094	3,421	12,301	18,185	8,044	106,062

National Institute of Child Health and Human Development

Budget Mechanism

	1975[A] Number	1975[A] FTE[B]	1975[A] Amount	1976 Number	1976 FTE[B]	1976 Amount
Grants						
Regular						
Non-competing	603		$ 41,848,000	565		$ 42,399,000
Competing	110		6,022,000	44		2,484,000
New	375		22,581,000	85		5,073,000
Supplemental	(20)		400,000	(20)		400,000
Subtotal	1,088		70,851,000	694		50,356,000
Special						
Mental retardation research centers	12		5,608,000	12		5,608,000
Research career programs	71		1,839,000	71		1,839,000
Scientific evaluation	--		186,000	--		214,000
Subtotal	83		7,633,000	83		7,661,000
Total research grants	1,171		78,484,000	777		58,017,000
Fellowships						
Non-competing	160		2,197,000	235		3,421,000
Competing	--		---	--		---
New	103		1,442,000	--		---
Supplemental	--		---	--		---
Subtotal	263		3,639,000	235		3,421,000
Training grants						
Non-competing	89	478	6,218,000	89	469	6,094,000
Competing	--		---	--		---
New	--		---	--		---
Supplemental	--		---	--		---
Subtotal	89	478	6,218,000	89	469	6,094,000
Intramural, laboratory and clinical research						
Laboratory and clinical research	--		10,715,000	--		12,301,000
Biometry and epidemiology	--		698,000	--		726,000
Research and development contracts	--		19,043,000	--		18,185,000
Research management and program services	--		7,270,000	--		7,318,000
Total	--		126,067,000	--		106,062,000

A/ Excludes 1973 appropriation restorations

B/ Full-time equivalents

Population

Authorizing Legislation: Public Health Service Act, Title IV, Parts E and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits	--	---	--	---	--	---
Other expenses	--	$45,039,000	--	$36,123,000	--	- $ 8,916,000
Total	--	45,039,000	--	36,123,000	--	- 8,916,000
Subactivities:						
Contraceptive Development	--	6,593,000	--	6,504,000	--	- 89,000
Contraceptive Evaluation	--	4,900,000	--	4,500,000	--	- 400,000
Directed Behavioral Research	--	3,300,000	--	3,000,000	--	- 300,000
Research Fundamental to the Population Sciences	--	30,246,000	--	22,119,000	--	- 8,127,000
Total	--	45,039,000	--	36,123,000	--	- 8,916,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	210	14,025,000	219	16,062,000	+ 9	+ 2,037,000
Competing	198	11,961,000	31	1,936,000	-167	- 10,025,000
Special	24	715,000	24	725,000	--	+ 10,000
Subtotal	432	26,701,000	274	18,723,000	-158	- 7,978,000
Fellowships	97	1,313,000	83	1,209,000	- 14	- 104,000
Training Grants	120A/	2,232,000	120A/	2,187,000	--	- 45,000
Research and Development Contracts	164	14,793,000	154	14,004,000	- 10	- 789,000
Total	--	45,039,000	--	36,123,000	--	- 8,916,000

A/Full-time equivalents

Introduction

The Center for Population Research (CPR) within the National Institute of Child Health and Human Development (NICHD) is the principal Federal agency supporting research on fertility, reproduction, contraception, and the effects of population growth and change. The four major areas of concentration are 1) fundamental research in reproductive biology and the behavioral sciences, 2) the development of an array of contraceptive methods, 3) the evaluation of the medical effects of contraceptives in use, and 4) research in the social sciences which by collection and analysis of information about people and society will help us understand, on a rational basis, the causes and effects of population growth, change and distribution.

The population research program is accomplished through the award of research grants, including the Population Research Centers; fellowships; training grants; and research contracts; and the conduct of intramural research. The funds and description of programs for the intramural research effort are contained within the activity Intramural, Laboratory and Clinical Research. The funds to support the staff necessary to provide the scientific and administrative management of the population program are contained within the activity Research Management and Program Services.

Program Plans, 1976

Contraceptive Development - In 1976, clinical trials will be initiated in a major effort for development of contraceptive agents for men. Related to this applied work which shows promise after limited trials in humans, additional research will be initiated to identify new functional points at which male fertility can be interrupted. Drugs which can produce interference at such points will be sought.

Although the development of new contraceptive agents is the major goal of contraceptive development programs, the possibility exists that the safety of present oral contraceptives and the effectiveness of naturally occurring hormones can be improved through imaginative formulation techniques. These investigations will be initiated in 1976.

To improve the efficacy of natural family planning, additional effort in 1976 will be directed to development of reliable chemical and biophysical methods for the prediction and detection of human ovulation.

All of the compounds emanating from the synthetic hormone program, as well as compounds from other sources, are being evaluated continually for their contraceptive utility. To optimize advanced stages of the drug development program, a new primate (baboon) investigation effort will be initiated by scientists in 1976. Its primary aim is to assess the contraceptive efficacy of the synthetic estrogens developed in 1974 and 1975.

Contraceptive Evaluation - The focus in 1976 for evaluation of contraceptive techniques in use will be the expansion of several areas of the ongoing program.

Ongoing studies of the effects of oral contraceptives in various animal species will provide a basis for assessing their usefulness in predicting effects in man. Comparative studies of the metabolism of contraceptive steroids in dogs, monkeys, rodents and man will provide data on species differences in breakdown and excretion of the drugs. Research to identify the risk factors which might predict a hypertensive response among users of oral contraceptives may lead to more knowledgeable and safer prescribing of such medications. Research will be done to evaluate how successfully hypertension may be reversed or treated following discontinuation of oral contraceptive steroids.

Concerns about the safety of various intrauterine devices, now estimated to be used for birth control by more than three million women in this country, require that authoritative research provide data to describe the risk of specific severe complications, including maternal deaths, for all IUDs currently in use. It is also expected to identify subpopulations of women who may be at high risk in regard to socioeconomic, demographic and biological characteristics.

Data are expected from follow-up studies of a large series of men vasectomized over the past several years to determine their medical status. These data will provide rough estimates of possible medical consequences of vasectomy and may identify additional research needs.

Behavioral Sciences Research - Increased attention will be given to research which can yield organized and consistent data concerning the economic and environmental consequences of population change. In a period of growing debate on development and distribution of resources such as food and oil, the population factor is increasingly identified as a most important variable. It is essential that considerations of the population factor have a rational and scientific data base in these debates and not be poorly based on irrational conjecture. This research is aimed toward development of such data.

Teenage pregnancies continue to increase in relation to total pregnancies in a period of declining U.S. birth rates. Additional research is planned to identify reasons for this serious social problem and to suggest possible solutions.

The relationship between the status of women, especially their employment status, and their fertility will receive further attention. Early labor-force participation, type of work, career aspirations, social and psychological pressures, career selection, and job status are factors which appear to affect fertility decisions. While approximately twenty-three percent of all white married women with a child under five worked in 1970, thirty-four percent of those women who had more than a college education worked. Other studies will investigate the extent to which this is the result of greater commitment to a career, greater ability to pay for childcare services, or other factors.

Results from a study of the values associated with family size suggest that the anticipated reward of children is the most important in the initiation of family building, but the recognition of the costs of children is most important in the decision to terminate family growth. Another investigation found that, relative to income, the cost of children is less the higher the income. The poor not only have more children, but relative to means, pay more for them. Studies on the costs and values of children will focus not only on the monetary costs, but on the physical, psychological and social costs for parents.

Research Fundamental to the Population Sciences - In addition to continued support of increasingly sophisticated and complex reproductive biology and endocrinology studies, and broad basic population processes in the social sciences, the activities of the program include a productive Population Centers program. These Centers in the aggregate provide a coordinated, multi-disciplinary resource of scientists working on fundamental social and biomedical population research concerns. Twelve Centers are currently supported by this four year old program.

More progress has been made recently in understanding the control of sperm production than in the past several decades. Sperm production is controlled by the two male sex hormones, testosterone and follicle stimulating hormones (FSH). Testosterone stimulates sperm production directly and is aided in that action by FSH which causes the production of a protein (Androgen Binding Protein - ABP) which carries the testosterone to those parts of the testis where sperm are produced. This new information suggests three possibilities for the development of male contraceptives. Such a new contraceptive might act by preventing the transportation of testosterone by ABP by blocking the binding of the hormone to the protein. Secondly, it might be possible to develop a male contraceptive which acts by blocking the secretion of FSH by the pituitary gland. Thirdly, the clarification of the role of FSH in sperm production affords opportunity for development of a male contraceptive measure based on blockade of the production of the ABP required for testosterone action. Such research leads will be pursued.

Program Plans, 1975

Contraceptive Development - Efforts to produce better chemical contraceptives for both men and women will continue with increasing intensity. Estrogens (female sex hormones) are potent antifertility agents in experimental animals as well as in man and form an essential part of most of the oral contraceptives presently on the market. However, estrogens often are associated with a number of unpleasant medical effects, and, in a few women, present real health hazards. To effect a separation of antifertility from estrogenic activity is a major program goal. In this connection, a class of compounds related to estrogen appear promising. Studies are underway in two species of primates to assess the clinical potential of two of these compounds. Information relating to these studies is expected to be available during 1975. If promising results are obtained, preclinical drug safety studies will be initiated which will allow their evaluation in man. Within the same class of compounds further synthetic work is in progress to find modifications having even greater separations of antifertility and estrogenic activity.

The initial clinical trial of chemical contraceptives for men was completed in 1974. This work involved the daily oral administration of a weak synthetic male hormone combined with a once-a-month injection of a potent synthetic male hormone. In the majority of men, sperm numbers decreased to very low levels after about two months of therapy. Such low sperm numbers are believed to be incompatible with fertility. Following cessation of the six months therapy, sperm numbers return to normal levels in about six weeks. None of the men exhibited undesirable medical effects, which lends support to the feasibility of this approach. In 1975, the program plans expansion of these studies and the search for new male antifertility chemicals.

The development of new drug delivery systems aims for development of biodegradable polymers within which contraceptive drugs may be placed.

Theoretically, such a system should deliver the drug at a predetermined steady rate over long periods of time and thus eliminate the necessity for daily administration. Since the polymer degrades slowly in the body to harmless constituents, it does not have to be removed from the body after the drug has been exhausted. Several such polymers have been formulated and their properties are being evaluated in vitro and in animals.

Two new intrauterine devices (IUDs) are being evaluated. An IUD which releases very small amounts of the female sex hormone, estriol, has been tested in the rabbit. The device without the hormone has no effect on fertility, whereas the device releasing estriol was totally effective. This IUD is being tested in baboons to establish the level of the drug that should be released in the uterine cavity without having an effect on other body organs.

A soft fluid-filled IUD has been tested in one hundred women volunteers. The initial trial has produced encouraging results and the testing program is being expanded to an additional two hundred subjects. The program plans to compare this IUD to presently marketed IUDs in simultaneous clinical trials.

The device program also aims at making vasectomies or vasal occlusions easily reversible. Several types of devices are undergoing extensive evaluation in a variety of laboratory animals and successful reversal of the infertile condition to a fertile state has been accomplished. It is still too early to predict the successful utility of this approach to men, but in 1975 a decision will be made on the merits of this approach to human fertility regulation.

Contraceptive Evaluation - This program has focused on evaluating effects of two methods of contraception, oral contraceptives and vasectomy. In 1975 and 1976 it is intended to expand the scope of this program to involve other important methods such as IUDs.

The long term surveillance of a large population of women taking contraceptive steroids has revealed effects of these contraceptive steroids on several parameters known to be risk factors in cardiovascular disease. Thus, contraceptive steroids result in a six-fold increase in risk of hypertension among its users. Also these contraceptives produce a decrease in glucose tolerance, an increase in body weight, and effect on blood coagulation in the direction of hypercoagulability and an increase in certain blood lipids.

The continuing surveillance of this population is designed to identify to what extent such effects on risk factors identify subpopulations of oral contraceptive users likely to develop cardiovascular complications later in life.

Surveys of biochemical nutritional parameters in contraceptive users have identified three potentially important problem areas. The findings suggest a tendency among oral contraceptive users towards vitamin B6, folic acid and zinc deficiencies. Further investigation will attempt to identify the clinical significance of these observations.

A series of new projects has been developed to pursue the relationships, if any, between various contraceptive agents and methods currently in use and the occurrence of birth defects. These projects consist of evaluations of oral contraceptives, the rhythm method, the use of the various spermicidal agents and of IUDs. The studies include prospective and retrospective investigations not only of specific malformations which are suspected of being associated with contraceptive steroids like congenital heart disease and malformations of the limb but also other types of malformations.

Studies to determine the possible consequences of vasectomy in man and laboratory animals are continuing. Blood specimens from patients before and at two and nine months after vasectomy have demonstrated two kinds of antibodies to sperm: one type is present in half the patients before vasectomy and increases somewhat in amount two months after the operations but shows little subsequent change. The other type is rare before vasectomy and increases in incidence the longer the interval after the operation. These two types of antibodies are directed to antigens on different regions of the sperm surface. The possible medical significance of these antibodies will be investigated.

Behavioral Sciences Research - The goals of the behavioral sciences program in population research are: (1) to ascertain the social, psychological, and economic determinants of fertility in the U.S. and (2) to assess the consequences of population growth and change.

In fertility research, several new studies are being undertaken to determine the factors which influence the selection and use of contraceptive methods. The National Fertility Survey of 1970 reported that twenty-six percent of couples who use contraception report that within their first year of exposure to risk they fail to delay a pregnancy which they wish to have at a later time, but only fourteen percent fail in preventing a birth they did not want at any time.

Between 1970 and 1971, teenage illegitimacy dropped ten percent in states with liberalized abortion policies but rose slightly (0.3 percent) in the non-abortion states. Given the earlier similarity in illegitimacy rates, this subsequent divergence suggests that legal abortion was a major factor in the nationwide decline in teenage illegitimacy between 1970 and 1971. In 1971, legal abortion not only influenced teenage illegitimate birth rates, but for white teenagers, legitimate birth rates as well. White teenagers were the only group of women to experience rising legitimate birth rates between 1965 and 1970, but in 1971 their marital fertility declined in abortion states and continued to rise in nonabortion states. Because the fertility of married teenagers reflects the influence of conceptions before marriage, this decline indicates that legal abortion may have also reduced the incidence of forced teenage marriages. On the whole, legal abortion was of key significance in teenage reproduction in 1971.

There is evidence that variations in economic distress have played a significant part in the rise and fall of fertility since World War II. The findings support the hypothesis that the post-war baby boom arose from circumstances that produced a feeling of unusual affluence among young adults. In contrast young adults since the early 1960's whose fertility has declined, have found it much harder to realize their material aspirations, since they grew up during the much more prosperous conditions of the 1950's. It appears reasonable to assume that such developments as the oral contraceptives and the women's liberation movement may have reinforced the impact of changing economic stress in inducing a decline in fertility. New studies have been initiated to further examine the social and economic determinants of fertility trends in the U.S. between 1940 and 1970 - the period of the baby boom and the subsequent decline in fertility.

Research Fundamental to the Population Sciences - The basic research which may provide the most significant new leads for contraceptive development in the near future is aimed at the elucidation of the mechanism of hormone action in general and sex steroid hormone action in particular. Through the feedback interaction with the hypothalamus and pituitary gland, those hormones are

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intimately involved in the control of such reproductively essential phenomena as the ovarian and menstrual cycles, ovulation, sperm development and acquisition of fertilizing ability, gamete transport, preparation of the uterus and subsequent implantation, embryo development and parturition. Such involvement by sex steroid hormones in the control of reproductive processes is possible because cells in the tissues, organs and systems in which such processes occur exhibit a special sensitivity to the hormones and respond to them in a unique manner. Hormones bind themselves to specific proteins called receptors in such target organs as ovaries, testes, and the uterus. The structure of these receptors, especially for estrogens and progesterone, is being studied since it could be possible to interfere with steroid-receptor interactions to decrease fertility.

A final example of important new developments is the great deal of progress made in research on luteinizing hormone releasing factor (LRF), a substance which indirectly causes ovulation by stimulating the release of another hormone (LH). Much of this research is aimed at the manufacture of LRF-like substances which will block the action of LRF in the induction of ovulation and the use of such substances in causing ovulation to occur at a predictable time. Some of these synthetic substances are as much as 280 times more potent than LRF. Synthetic LRF-like substances may prove to be of great value in both fertility regulation and alleviation of infertility. They may prevent ovulation by blocking the normal response of LH to LRF stimulation. They promise to improve the reliability of the rhythm method by fixing the time of ovulation and thereby defining a truly safe period.

The Population Research Centers provide a coordinated, multidisciplinary approach to fundamental research on the reproductive process. In 1975, two new Population Research Centers were added to the Centers' network. There are now twelve Centers. The new Princeton University Center will concentrate its research efforts on demography and the new University of Pittsburgh Center is undertaking an intensive research endeavor in primate reproduction.

Population Centers	Locations
Vanderbilt University	Nashville, Tennessee
University of Texas at Austin	Austin, Texas
Population Council at the Rockefeller University	New York, New York
University of Wisconsin	Madison, Wisconsin
University of Chicago	Chicago, Illinois
Harvard University	Cambridge, Massachusetts
Johns Hopkins University	Baltimore, Maryland
Baylor Medical College	Houston, Texas
University of North Carolina	Chapel Hill, North Carolina
Columbia University	New York, New York
Princeton University	Princeton, New Jersey
University of Pittsburgh	Pittsburgh, Pennsylvania

Child Health

Authorizing Legislation: Public Health Service Act, Title IV, Parts E and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits	--	---	--	---	--	---
Other expenses	--	$62,345,000	--	$49,594,000	--	-$12,751,000
Total	--	62,345,000	--	49,594,000	--	- 12,751,000
Subactivities:						
Perinatal Biology and Infant Mortality	--	20,796,000	--	16,872,000	--	- 3,924,000
Growth and Development	--	20,379,000	--	15,002,000	--	- 5,377,000
Mental Retardation	--	21,170,000	--	17,720,000	--	- 3,450,000
Total	--	62,345,000	--	49,594,000	--	- 12,751,000
Budget Mechanism:						
Research Grants:						
Regular:						
Noncompeting	393	27,823,000	346	26,337,000	- 47	- 1,486,000
Competing	287	17,042,000	98	6,021,000	-189	- 11,021,000
Special	59	6,918,000	59	6,936,000	--	+ 18,000
Subtotal	739	51,783,000	503	39,294,000	-236	- 12,489,000
Fellowships	166	2,326,000	152	2,212,000	- 14	- 114,000
Training Grants	358A/	3,986,000	349A/	3,907,000	- 9	- 79,000
Research and Development Contracts	40	4,250,000	39	4,181,000	- 1	- 69,000
Total	--	62,345,000	--	49,594,000	--	- 12,751,000

A/ Full-time equivalents

Introduction

The goal of the Child Health program is to improve the health and well-being of mothers and children throughout their life span, from conception into adulthood. The newly established Center for Research for Mothers and Children carries out this program through both biomedical and behavioral research. The focus on infant mortality and morbidity is of primary importance because of the tragedy of mortality, and the fact that morbidity at one stage in the life-span often predisposes diseases later in life. Research fields include the health of the mother; the effect of her health on the child both before and after birth; and the survival and well-being of the child through the hazards of intrauterine life, the birth process, and the adjustments to the new extrauterine environment. Attention then moves to the investigation of social, psychological, nutritional, hormonal, genetic and other factors relating to growth and development into adulthood. Abnormal development and mental retardation are studied in conjunction with the normal development of infants, children, and youth.

The child health research program is accomplished through the award of research grants, including Mental Retardation Research Centers; fellowships; training grants; and research and development contracts; and the conduct of intramural research. The funds and description of programs for the intramural research effort are contained within the activity Intramural, Laboratory and Clinical Research. The funds to support the staff necessary to provide the scientific and administrative management of the child health programs are contained within the activity Research Management and Program Services.

Perinatal Biology and Infant Mortality

The perinatal biology and infant mortality program is committed to the promotion of a coordinated research effort which will enhance understanding and development of knowledge as related to maternal health, pregnancy, embryonic development, fetal growth, and infant well-being through the first year of life. Research activities are also directed toward ameliorating infant morbidity, preventing infant death, and narrowing the gap between the identification of new knowledge and its incorporation into health care delivery.

In 1973, there were slightly more than 3.13 million live births. About 238,000 of these infants (7.6 percent) were born weighing less than 5.5 pounds. Between 40,000 and 42,000 of these babies die within the first month of life and account for about 95 percent of all babies who die in this period. Infants who died between one month and one year of life brought the total of infant mortality to over 55,000. Of the more than 13,000 infants who died after one month of age, it is estimated that more than half succumbed to the sudden infant death syndrome.

In addition to being the principal source of neonatal mortality, low birth weight infants who survive have the highest probability of being disabled for the balance of their lives, a burden to themselves, their parents, and often society. The low birth weight infant frequently derives from a mother who is adolescent, malnourished, or afflicted with chronic diseases such as toxemia and hypertension. Other high risk infants are born to mothers who have diabetes, a genetic disorder, or a poor reproductive history. Socio-economic factors are also important considerations, although low birth weight infants occur in all social classes.

The major human problems of cerebral palsy, mental retardation, sensory and cognitive disabilities, and a diminished ability to adapt socially, psychologically, and physically to an increasingly complex environment are some of the problems occurring in childhood and adolescence which have antecedents in early life and which diminish the self-sufficiency of afflicted adults.

Program Plans, 1976

Program efforts will concentrate on three major contributors to infant morbidity and mortality: low birth weight, the sudden infant death syndrome, and congenital malformations.

To reduce the incidence of low birth weight infants it is essential to expand our understanding of why some of these babies are born prematurely while others suffer from intrauterine malnutrition. Major emphasis will be given to investigations which are attempting to unravel the mystery of the premature initiation of labor. Labor that begins too soon is the major cause of low birth weight. Evidence is accumulating that (1) the fetus may play a significant role in triggering the birth process, and (2) labor begins because the metabolic capacity of the uterus and placenta can no longer cope with the metabolic demands of the fetus. These two hypotheses will be explored further in 1976. In addition, investigations will be undertaken to determine why one-third of all low birth weight infants suffer from intrauterine malnutrition which has stunted their growth and neurological capacity. Success in combating low birth weight will make it possible to prevent the neurologic and physiologic deficiencies that are its most frequent consequence.

Efforts also aim to identify the infant at risk for the sudden infant death syndrome and to prevent its occurrence through continued expansion of current research efforts as well as the establishment of case registers for infants at risk for SIDS. Babies who have been observed both in the nursery and at home to stop breathing for short periods at frequent intervals sometimes become victims of the sudden infant death syndrome. It is essential to understand the physiologic antecedents of frequent nonbreathing episodes (apnea) and to determine if there is a cause and effect relationship between this periodic apnea and susceptibility to crib death. A national case register for such cases could contribute significantly to identifying infants at risk and instituting preventive measures.

Another major objective concerns congenital malformations. Approximately 3.5 percent of all babies born alive in this country show evidence of a defect at birth; by the end of the first year of life some 7 percent of infants have identifiable defects. Approximately 20 percent of infant mortality is attributed to defective development which has its beginning in utero.

The impact of sustaining defective children is immeasurable in both financial cost and emotional burden to the family and society. The need is for more fundamental studies of embryology development which will help to clarify the role of such environmental factors as viruses, drugs, nutrition, and heredity, singly and in combination, on the human embryo during the earliest stages of its development. A coordinated research program will be emphasized to cope with the problem and to enhance research efforts in pertinent areas.

Program Plans, 1975

Although there are many factors that contribute to low birth weight, prematurity (and the factors that cause prematurity) accounts for two-thirds of all low birth weight infants. Studies testing various hypotheses as to the controls on the duration of gestation and the events leading to the initiation of labor can offer leads to the solution of this problem. Efforts toward solving specific suspected causes and approaches to the prevention of low birth weight are being started. Studies examining the epidemiology of intrauterine growth retardation are being pursued to enable identification of pregnancies at risk of producing low birth weight infants. Intrauterine infectious diseases and other noxious environmental substances at various periods during pregnancy require continued scientific research.

It is now well known that infant morbidity and mortality can be increased by maternal disease and complications of pregnancy such as poor nutritional status, diabetes, high blood pressure, anemia, drug addiction, smoking, and the psychic stress of pregnancy. Scientific opportunities and expectations are encouraging for the health of the mother, child, and society. Research will continue to probe mechanisms to prevent these complications.

Another major research area focuses on the psychosocial dynamics of pregnancy. In contrast to the relative wealth of information available concerning the biological aspects of pregnancy and pregnancy outcome, there is a paucity of knowledge about the relationship of attitudes and behavior of parents and grandparents to pregnancy outcome. Questions about the relevancy to pregnancy outcome of parental feelings of emotion and economic security, including feelings about self-worth, are being explored. A new effort is directed toward identifying psychosocial factors operative during pregnancy, delivery, and the immediate post partum period which affect the fetus and newborn and which would contribute to infant morbidity and mortality.

Efforts are also continuing to understand the interplay of factors which determine the initiation of labor. Such information is necessary in order to insure optimal fetal development and to retard premature labor. In conjunction with this, research will continue with the development of a fetal risk index so that the risk state of the fetus at any time in labor can be assessed and corrective or preventive measures be applied as warranted. The extension of previously completed research directed toward diagnostic procedures for monitoring the process of birth are being undertaken so that the prevention of aberrant states may be fully realized.

New leads have evolved that indicate that the sudden infant death syndrome could be related to: heart rate changes, apnea, and infection; lack of sleep; oxygen deficiency; abnormality in the brain stem; developmental maturational lag; immaturity of the nervous mechanism controlling heart function; and inadequate lung responses. Research is exploring these new leads. Specific avenues of research in 1975 include the distribution of SIDS within the population and characteristics surrounding its occurrence; identification of infants at high risk; studies of the structural and functional changes in tissues and organs which may be involved in SIDS; and the psychological stresses experienced by the family and the community in which SIDS occurs.

An important part of the SIDS endeavor is to inform the professional and lay communities about the problem and the approaches that are being taken to identify the underlying mechanism. The scientific information endeavor, consisting primarily of workshops and publications, is being continued. It is a multifaceted effort that must encourage scientists to pursue research as well as to educate members of society - physicians, nurses, clergy, friends and families of SIDS victims, rescue workers, and others - to understand the problem and not show hostility toward the bereaved family.

Growth and Development

The growth and development program encompasses developmental research on the child, from infancy through adolescence to maturity. Behavioral and biomedical aspects of child health and development are included within the scope of this program, but especially emphasized is multidisciplinary research which integrates both of these major research approaches. Time-related changes in factors (both within the individual and in his physical and social environment) which direct in important ways the development of the individual are topics of investigation. The ultimate goal of research supported by this program is to help the child become an independent, healthy, and productive adult member of society.

According to 1970 census data, of the 73 million children between 10 and 18 years of age in this country, fully 7 million are handicapped in some major way. These handicaps include communicative disorders and learning disabilities, retarded growth, obesity, reduced ability to withstand disease, and behavioral problems of a serious nature. Any of these disorders may serve to prevent the individual from assuming a fully functional adult role. The growth and development activity, through its support of studies of normal growth and development, aims toward an understanding of developmental disorders in order ultimately either to prevent or ameliorate them.

Program Plans, 1976

Scientists have recently identified several major health related problem areas in childhood which require special attention and basic research support. In some of these areas it will be necessary and appropriate to continue research into the mechanisms of normal growth and development to provide the much needed basic information and base-line data from which defects and abnormalities may be diagnosed and understood. In other areas it will be possible to turn the research support directly toward certain specific problems of childhood.

The current Recommended Dietary Allowances (RDA) of the Food and Nutrition Board, National Academy of Science are based on inadequate definitive information for any age groups and pertain by definition only to healthy individuals. There is a large number of children who suffer from chronic health problems during the growth period. Whether or not the nutritional requirements of these individuals are modified by their condition is not known. While the RDAs (which allows for some biological variability and a margin of safety) for most nutrients are quite likely adequate for children with chronic health problems, there is considerable circumstantial and some scientific evidence that many chronic conditions become acute coincidentally with periods of rapid growth. Thus, it would appear that chronic illness may increase needs for specific nutrients;

conversely deficiencies in specific nutrients may compromise biological development, physical performance capacity or cognitive ability. At the very least, if current RDAs are marginal or inadequate in terms of any nutrient, growth and development of affected children could be delayed and resistance to infection reduced.

In practically every classroom (and pediatrician's office) in the nation, children are found who suffer from learning disabilities. These children do not necessarily suffer from mental retardation or lack of general capacity as measured by IQ. While performing quite well in some academic and social areas, they may have a specific reading disability (dyslexia, word blindness), a special language dysfunction or delayed language or speech development. It is important to investigate the genetic, embryonic-developmental, nutritional, neurophysiological and biochemical components of these problems as well as the way social factors such as parenting, teaching and environment affect these unfortunate children.

The poignant problem of chronic illness in childhood has become increasingly prevalent, owing, in part, to the very successes of modern medical technology. Chronic illness is arbitrarily defined as a disease condition lasting longer than one year; most chronic childhood illnesses are also characterized by periodic exacerbations and high intensities of medical involvement. The growth and development program will attack current major health problems in a broadly-based program of research to discover developmental causes of these chronic conditions and ways to reduce their prevalence. Furthermore, medical advances have made it possible to maintain the life of chronically ill parents and children, often with potentially disrupting effect on non-ill children and on family function or cohesion. This relatively unstudied problem will be aggressively pursued.

Scientists also will be engaged in studying a central biological question: the control of the flow of genetic information during growth and differentiation. Specifically, programs will be expanded in the following areas: (a) chromosomal disorders, such as Klinefelter's Syndrome, Turner's Syndrome; (b) human genetic diseases, such as inborn errors of metabolism and sporadic cretinism; and (c) congenital anomalies, such as myelodysplasis.

Program Plans, 1975

During 1975 the growth and development activity is continuing its nutrition research efforts. This research is closely coordinated with the nutritional research being pursued in other programs of the Institute; especially, mental retardation and perinatal biology and infant mortality. Through such coordination, there is an optimal utilization of resources of the Institute to produce accomplishments for all child health endeavors. Nutrition studies have examined the role of undernutrition in physiological and intellectual development, the impact of pre and postnatal malnutrition on the development of immune competency and illness in children, and the interactions between nutrition, behavior and environment. This research effort has resulted in new knowledge regarding the adverse impact of malnutrition in pregnancy in terms of the development of the progeny and data are now becoming available concerning the beneficial effects of nutritional supplementation during pregnancy on child development. Recent research has also provided an improved description of physical growth and body composition in relation to the age, sex, and nutrient intakes of normal infants receiving either breast milk or cow's milk. The fact

that adipose (fat) tissue develops early in childhood, if not in the fetus itself, suggests mechanisms by which obesity in young children predispose them to adult obesity. The need for early intervention programs is apparent. The Institute also is exploring the behavioral factors in obesity which make the treatment of adult obesity so difficult.

A thorough review of all available data bearing on physical growth of children of the major ethnic groups in the U.S. indicates that the various races do not differ in growth up to eight years of age, given optimal health care and an adequate socioeconomic environment. Thus, this research shows that physicians, public health personnel, and other clinic staff do not need individual race-specific growth charts to assess the child's development or evaluate the impact of intervention programs. Due to the complexities of pubertal development we can not yet be certain whether this observation also holds thoughout the adolescent period.

Thousands of children in this country suffer from pituitary insufficiency of growth hormone; without injections of this vital substance they would be permanently dwarfed, usually not growing above 4 feet in height. Research is underway to determine the active portion of the large growth hormone molecule so that eventually it can be synthesized rather than procured in insufficient amounts from human pituitaries. It has been found that one fragment that retains activity consists of 114 amino acids rather than the total of 191, so the goal of synthesis is considerably closer. This research is directed toward a better understanding of the fundamental factors which initiate and control the process of orderly growth and development at a molecular and cellular level. It is also devoted to a study of the development of normal physiological functions and processes of control, and the flow of information between cells and the whole organism.

During 1975 the growth and development program has continued to investigate the immunologic mechanisms used by the human host to combat disease, infectious agents, and foreign substances, and the ability to recognize the tissues of the host so as not to produce destructive autoantibodies. Special attention in this program has been given to the development of immunologic competence as a function of age with an emphasis on the newborn and infant, but with a continuing interest in older age groups as well. Recent research progress makes it increasingly apparent that the impact of immunologic mechanisms for combating infections and foreign substances (such as environmental pollutants, and drugs) on the development of the immune response in early life may also program response to disease in adulthood and aging.

In the area of learning, cognitive development and human communication, research efforts are directed toward a better understanding of the learning process, the way individuals acquire or modify knowledge, skills and habits, and a better understanding of the processes that are involved in the development of normal communicative skills as well as those factors which may interfere with normal development. The current emphasis is both on the learning process in general and more specifically studies of the acquisition of such skills as speech, language, and reading. It has often been assumed that one of the reasons it is so difficult for many children in this country to learn to read is that English is not a very phonetic language. Many words are simply not spelled the way they sound.

While various orthographies (letter shapes) and revised spelling systems have been proposed to improve reading instruction, it has been difficult to test their effectiveness in a natural setting. Recently an unusually interesting research project has been initiated taking advantage of the fact that in Yugoslavia the Serbo-Croation language is written in two orthographies, Roman and Cyrillic. A number of experiments are now being conducted which are focused on the basic processes used by readers in letter and word recognition. The experiments take advantage of the fact that both Cyrillic and Roman alphabets are entirely phonetic and each is read with equal facility. These projects should provide significant knowledge concerning how children might most efficiently be taught to read, and improved diagnostic and remedial procedures for those who have reading disorders.

In the research effort to study personality and social development, investigators have continued to examine the growth and differentiation of self-concept, the acquisition of values and behavioral controls, the nature and development of the personality and the effects of early experience on all of these. A study of patterns of parental authority found, in general, that authoritative parents (combining firm control, warmth, rationality, and receptivity to the child's communication) are most likely to facilitate the development of competence (responsible and independent behavior) in young children in contrast to parents who are either authoritarian or permissive. Scientists have already determined that there are significant sex, race, social class, and individual differences in the self-concept, a psychological variable which influences such other variables as achievement motivation, level of satisfaction and degree of success in the development of appropriate adult roles. Preliminary findings indicate that certain critical biological, psychological and social events occurring during adolescence may be involved in the development of self-esteem. These include, among others, physical size for age, communicative skills, age at onset of puberty, and the psychosocial context in which these events occur.

Research efforts have continued in 1975 toward an improved description of the effects of early experiences upon the developing brain and behavior, and a better understanding of the neurobiological mechanisms that mediate social, emotional and intellective behaviors. The results of recent research appear to indicate that early sensory experiences both pleasurable and painful may have long lasting effects on both the biological and psychological development of the human.

Mental Retardation

Mental retardation ranks as a major national health, social, and economic problem. The effects of mental retardation are chronic and, when incorrectable, endure throughout the life span of afflicted individuals while presenting significant research and treatment problems at all age levels from conception to maturity. The economic costs to the nation of mental retardation, estimated at over $3 billion annually, are staggering; the cost to afflicted individuals and their families is beyond measure. Over 20 million Americans, representing the families of our nation's more than 6 million mentally retarded persons, are directly affected by the problem of mental retardation. They know and bear its full impact--its economic toll, its pain, its effect on social and human values. Research leading to the prevention of the complex and multifaceted problem of mental retardation is the key to its ultimate resolution.

The causes of mental retardation are biological, social and psychological in origin, sometimes acting singly, more often in combination. They include inborn errors of metabolism as in phenylketonuria or galactosemia; disorders of maternal health during pregnancy; possibly chromosome abnormalities as in mongolism; endocrine dysfunction; possibly malnutrition; and the many family and environmental inadequacies associated with poverty and depriving life situations.

Program Plans, 1976

Research into the causes, means of prevention, and methods of amelioration of mental retardation serves many of the research requirements of the developmental disabilities including cerebral palsy, epilepsy, autism and special learning disabilities. With the exception of special learning disabilities, mental retardation is frequently associated with the other developmental disabilities.

These conditions are a frequent consequence of reproductive casualty resulting from disorders of pregnancy, complications of birth, and maternal ill health. The Institute, because of its assigned responsibility for research in maternal and child health, has a major research concern for these disorders. All of the Institute's Child Health endeavors, including its intramural research program, make significant contributions concerned with these issues.

The mental retardation program will continue to support research into the biological, behavioral and social processes which contribute to or influence the development of retarding disorders. Of primary concern are basic studies into the causes and means of preventing mental retardation. These research programs provide knowledge and understanding applicable not only to the problem of mental retardation but to other closely related developmental disabilities as well.

Many of the research accomplishments have been achieved in the 12 Mental Retardation Research Centers supported by the Institute. These interdisciplinary Centers, located throughout the country, are uniquely capable of investigating the complex problems of mental retardation and related developmental disabilities, training of future scientists, and applying research findings to service. Together, these Centers represent a major national resource for research aimed at finding the means of prevention and amelioration of mental retardation and related developmental disabilities. In 1975 and 1976 there will be approximately 600 investigators and 1,200 support personnel working in these Centers:

Centers	Locations
University of Chicago	Chicago, Illinois
Children's Hospital	Cincinnati, Ohio
George Peabody College for Teachers	Nashville, Tennessee
University of Colorado Medical Center	Denver, Colorado
University of Washington	Seattle, Washington
University of California at Los Angeles	Los Angeles, California

Centers	Locations
Albert Einstein College of Medicine	Yeshiva University, New York, New York
University of Kansas	Lawrence, Kansas
Walter E. Fernald State School	Waltham, Massachusetts
Children's Hospital Medical Center	Boston, Massachusetts
University of North Carolina	Chapel Hill, North Carolina
University of Wisconsin	Madison, Wisconsin

In 1976, both within and outside of the Mental Retardation Research Centers, scientists will be conducting research toward both the prevention and amelioration of mental retardation.

Down's syndrome is the largest single category in mental retardation of organic origin. Lowering the incidence of Down's syndrome (mongolism) is a primary Institute goal. Many separate investigations have contributed to advances which have made possible the diagnosis of mongolism during the early months of pregnancy. Collectively, these advances across the broad fields of genetics, cytogenetics, and obstetrics have established the technology for service programs of intrauterine diagnosis. Prevention of mongolism and other genetically determined disorders is now possible through utilization of these new diagnostic capabilities. Provided with an accurate diagnosis during early pregnancy, and assisted by genetic counseling, the parents of an abnormally developing fetus can elect termination or continuation of the pregnancy.

Other specific genetic diseases, while less common than Down's syndrome, together constitute a significant aspect of mental retardation disorders. Research into the mechanisms by which virus genes are incorporated into host cells, the more accurate assessment of chromosomal abnormalities, the mapping of human structural and regulator genes through linkage studies and other techniques and the behavioral significance of minor abnormalities are some of the important areas to be continued and expanded in 1976. Continuing research into the relationship of nutrition and intellectual development and brain growth indicates the issues are more complex than previously thought. A study of the effects of wheat as a sole protein source during pregnancy and its effect on the brain development of rats demonstrated that fortification with lysine or lysine plus threonine markedly improves brain growth. If duplicated in clinical research, these findings have international importance because of the frequent use of lysine deficient staples in developing countries.

An examination of children in Head Start who fell below the third percentile in height and weight indicated deficiencies in zinc, vitamins A & D and folic acid. This suggests the need for careful nutritional evaluation of children with these physical traits, and investigation of dietary supplementation to influence child development.

Micronutrients in the diet too, such as chromium and zinc, are assuming increasing importance as factors in development and disease. Chromium deficiency has been identified as causative or contributory to glucose intolerance of children suffering from protein-calorie malnutrition and to the onset of

diabetes in middle-aged and elderly persons. Low birth weight may also be associated with this deficiency. Further confirmation in 1976 of these findings may require modification of current dietary practices and food processing techniques.

Investigators have also studied the use of nutritional aids to improve the nutritional status of migrant farm children. Success was marginal despite the favorable ratio of aides to families and extensive professional training and support. This study indicates that simple remedial solutions to problems of malnutrition may not be effective, and further research will be undertaken on ways to change dietary habits.

These findings are augmented by other studies in experimental animals and intervention efforts with undernourished children and pregnant women throughout the world. It is increasingly apparent that the potential behavioral and intellectual consequences of long-term malnutrition will require a combined nutritional, educational, and public health intervention to be most effective. These relationships will be further explored in 1976.

In the area of amelioration of mental retardation the research accomplishments and leads described in 1975 will be pursued further in 1976. Scientific behavior management systems will undergo additional investigation so that appropriate clinical utilization can be achieved. In addition, since mental retardation is always expressed as a factor of mental or brain dysfunction, the learning accomplishments of the past must be examined to develop optimal training or learning, and testing procedures.

Studies of home as well as institutional management of the mentally retarded will be continued in 1976 because the immediate impact of mental retardation today is felt in these environments. As an example, research will attempt to identify the personality traits of caretaker personnel conducive to resident-oriented care practices, because these practices have recently been proven successful in helping retarded individuals intellectually, emotionally, and physically.

Program Plans, 1975

Varying estimates have been made on the incidence of genetic disease concerning mental retardation. One estimate indicates that more than 2 percent of the population suffers from diseases or congenital defects which are inherited according to Mendelian laws. Another 5 percent have disorders in which both environment and heredity tend to be associated with the development of the disease. This area of neglect is being pursued in 1975.

Research investigators have shown that the incidence of mongolism rises with increasing maternal age. The chances of giving birth to a child with mongolism is about five times higher for women over 35. It is over 35 times more frequent for women 45 or older. This has prompted the Institute to initiate a national health education campaign aimed at reducing the incidence of mongolism. Three pamphlets were developed and distributed to the medical and health related fields to assist in this effort. The Institute also sponsored a science writers seminar in an effort to bring to the public, through the popular press, the important epidemiologic and genetic information which bears significantly on the incidence and prevention of mongolism. Research

leading to implementation of community-wide antenatal diagnostic and related treatment services to vulnerable women and the demonstration of an effective public health approach to prevention will be a priority of the Institute in the years ahead.

An organized multidisciplinary approach to the problems of intrauterine diagnosis will facilitate rapid development in the area of characterizing genetic and metabolic errors, in order to identify those disorders that can be diagnosed before birth. Program plans include follow-up on many promising areas of scientific opportunity as well as probing some of the most potentially productive scientific suggestions in this area, particularly: research dealing with gene localization and management of genetic disorders through organ transplantation; intergenic complementation and the use of bacterial viruses which contain the enzyme missing in a specific disease; and continued use of tissue culture which will help verify genetic heterogeneity and other important genetic factors.

Research at the genetic and cellular levels is combined with research at the organism and behavioral levels because of the complex interrelationships that all factors play in either producing or preventing retardation. Mental retardation many times is congenital and in many instances is found in conjunction with other congenital defects. Studies dealing with the mechanism of action of various agents causing congenital defects will continue.

Infectious diseases pose a major problem because of the difficulty in linking the infection with the damaged central nervous system. In addition to developing and applying vaccines to prevent infectious processes, scientists will also attempt to gain a better understanding about the so-called slow and latent viruses. Specifically, the etiology of Reye's syndrome, a potentially preventable condition characterized by vomiting, rapid development of coma, and convulsions generally following an acute infection, will be studied. Work concerning H. influenzae type b will continue because it is the most common etiologic agent in childhood. Meningitis, a disease that can cause mental retardation and other health problems, is the most common disease produced by this organism.

Although no direct causality has been demonstrated between malnutrition and human retarded intellectual development, highly suggestive evidence has been accumulated from numerous scientific investigations. Research is focusing on the improvement of early diagnosis of malnutrition.

Because of constraints imposed by the limitations of medical diagnostic procedures and development tests for infants, mental retardation is usually not detected early. Early diagnosis is critical because studies have provided evidence supporting the effectiveness of early intervention for improving the development of retarded children. Research, therefore, will continue in the areas of diagnosis and intervention so that appropriate early intervention will eventually be available for comprehensive clinical utilization.

In addition to intervention, treatment and amelioration programs are being continued. Excepting some inborn errors of metabolism such as PKU (phenylketonuria) and galastosemia, there are few remedies available today by which organic defects can be corrected. The search for treatments is being continued. For individuals who cannot be treated at present, the prevention of secondary handicaps or efforts to minimize the debilitating effects of the primary handicap through education, rehabilitation or training are major research goals. In the

final analysis, the amelioration or treatment of mental retardation involves helping the handicapped to a higher level of functioning and adaptation to the environment. The institutional environments for the severely retarded commonly deprive the patients of opportunities for social expression and meaningful human interactions, and not surprisingly, many individuals deteriorate even further in such a stultifying environment. Research leads that show positive results when such environments are altered are being followed-up.

The overwhelming majority of retarded persons are mildly handicapped and heavily concentrated in urban and rural ghettos. For these disadvantaged children, social environmental factors contribute to intellectual deficiencies and methods for remediating their effects constitute a major research effort. Investigators have developed a Responsive Teaching Model from research with such children which is now being applied in schools in nearly every state in the nation. The model, which is a scientific behavior management system, has been extended to the home and other settings with significant impact on social and academic behaviors of normal and handicapped children. The utilization of these techniques by parents should permit more developmentally disabled children to remain in their own homes and communities.

Investigators have also developed a successful program to allow severly and profoundly retarded children to communicate without the use of speech and language. Children in this experiment use geometric forms of various shapes as words and morphemes without requiring spoken responses. Such children are generally regarded as poor candidates for language training. Their potentials in this area are being further enhanced by the use of a motor imitation manual which serves as a basis for training in language skills. Many retarded children, partly because of impulsive behavior patterns, have difficulty in attending and learning. Studies of the effect of impulsiveness in retarded children indicate that learning does not take place even after weeks of training and that discrimination performance is poor under impulsive behavior. The introduction of a simple five second delay period dramatically increased receptive language performance, suggesting that in many situations learning ability of the retarded has been vastly underrated. The study points to the need for more research on optimal training and testing procedures in 1975 and 1976.

The trend toward maintaining severely handicapped children in their own homes demands a better understanding of family dynamics and its impact on development. Training of parents with children aged 18 months to 5 years has resulted in improved use of language and social competence in the child. Further studies in this area will have great value for implementing the Administration's program of deinstitutionalization and community-based services. An automated method for introducing severely retarded children to reading comprehension has been developed. Children are taught to associate dictated words with pictures and then with printed words. They can then associate pictures and printed words, thus learning a basic reading vocabulary. These preliminary steps to reading are accomplished by use of a teaching machine; the automated methods identify candidates for reading instructions who would otherwise largely be overlooked.

As part of the nation's growing concern with residential care, investigators are studying organizational and other elements affecting the quality of care in such facilities. Unitization--the establishment of quasi-autonomous living units in large formerly centralized institutions--is one of the elements under

study. Findings in one facility indicate only minor shifts toward resident orientation through such administrative change and that practices are still largely characterized by rigidity in routines, depersonalization and social distance between residents and staff. It has also been noted that IQ level of residents is strongly associated with the quality of care provided despite the higher staff ratios afforded the more severely disabled. This suggests the need to identify the personality traits of caretaker personnel conducive to resident-oriented care practices.

Intramural, Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act, Title IV, Parts E and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	188	$ 5,047,000	182	$ 5,267,000	- 6	+$ 220,000
Other expenses	--	6,366,000	--	7,760,000	--	+ 1,394,000
Total	188	11,413,000	182	13,027,000	- 6	+ 1,614,000
Budget Mechanism:						
Laboratory and Clinical Research	173	10,715,000	167	12,301,000	- 6	+ 1,586,000
Biometry and Epidemiology	15	698,000	15	726,000	--	+ 28,000
Total	188	11,413,000	182	13,027,000	- 6	+ 1,614,000

Introduction

The Intramural, Laboratory and Clinical Research program comprises the Institute's intramural effort, including biometry and epidemiology, in the major program areas of population and reproduction, and maternal and child health.

The Institute's laboratory and clinical research investigations cover the areas of population and reproduction, and maternal and child health. These investigations are conducted by scientists from two laboratories and five branches: the Laboratory of Biomedical Sciences, the Laboratory of Molecular Genetics, the Social and Behavioral Sciences Branch, the Pregnancy Research Branch, the Neonatal and Pediatric Medicine Branch, the Behavioral Biology Branch, and the Reproduction Research Branch.

Staff in the Office of Biometry and Epidemiology plan and conduct studies on diseases and conditions relevant to all programs of the Institute, particularly those that are quantitative in character. Emphasis is given to pregnancy outcome, newborn status, indices of infant well-being and adolescent problems. Clinical trials constitute a major area of activity. In addition, research in statistical methodology is undertaken. Consultation to other staff in the Institute is also provided.

Program Plans, 1976

Laboratory and Clinical Research:

Population and reproduction - In 1976, research efforts in reproductive

biology will continue to be directed toward developing the basic information and theory required for producing safer and ethically more acceptable methods of voluntary fertility control. These will include studies on the biology of sperm and egg production and transport, and the processes of fertilization and implantation, all of which might be manipulated for fertility control.

The number of men and women attending the infertility clinic is expected to continue to rise during 1976. Studying these patients not only sheds light on reproductive processes in health and disease, but also results in improved methods for diagnosis and treatment of human fertility problems.

Continued development and limited field trials of two assays developed in 1975 will be pursued in 1976. The first relates to a new more specific, more sensitive, and less expensive test for a hormone indicating pregnancy. The new test is superior to the one reported in 1974, but a limiting factor in its application has been a paucity of naturally occurring reagents. These reagents will be produced synthetically in 1976.

The second relates to the development in 1975 of a new, precise, efficient, and relatively inexpensive method for monitoring fetal health during gestation in high risk pregnancies, based upon following changes in concentrations of a hormone excreted in pregnant women's urine. Methods previously available were difficult to perform and expensive so that clinical applications were limited. If limited field trials now in progress support the usefulness of the determination more extensive use of the test in clinical practice can be anticipated.

Maternal and child health - In addition to laboratory investigations conducted by the staff of the Pregnancy Research Branch, intramural clinical research in the field of perinatal medicine will be initiated in 1976. Clinical investigators in the Pregnancy Research Branch and the newly established Neonatal and Pediatric Medicine Branch will admit pregnant women, newborn infants, and children for clinical investigation of disorders of pregnancy associated with high risk to mother and fetus. Diseases which contribute significantly to morbidity and mortality in newborn infants and children will be studied.

Promising leads, developed from studies in an appropriate animal model, will be followed up for use in preventing and treating a lung disease of premature infants (Hyaline Membrane Disease) that results in the death of 12,000 and disorders of the nervous system or intellectual impairment in 8,000 children each year in the USA. A limited field trial, already underway, will be continued.

Similarly, a lead concerning the role of milk sugar in regulating blood sugar levels in newborn animals will be followed up by limited clinical trials of this substance for treating low blood sugar in newborn human infants.

Finally, a collaborative field trial of a method for reducing death and permanent brain damage due to increased bile pigments in the blood of newborn infants will be continued.

Biometry and Epidemiology:

In 1976 the results of the study of amniocentesis will be a featured activity in the Biometry and Epidemiology program.

New studies in adolescence would assume more importance, and should move from a descriptive phase to analyses of high risk groups and etiologic relationships.

An analysis of the relationship between a history of induced abortion and subsequent ectopic pregnancies will take place. Preliminary analyses in the study of the effects of phototherapy in infants with bilirubinemia will be possible. In addition, staff will continue to provide statistical and epidemiologic support to all the Institute's programs.

Program Plans, 1975

Laboratory and Clinical Research:

Population and reproduction - Intramural population science consists primarily of research programs in reproductive biology with special emphasis on hormonal control of all phases of human reproduction from the development of sperm and eggs through fertilization and implantation to pregnancy and delivery. For this research, methods for measuring hormones are essential. During the past year several significant advances in methods for detecting and measuring hormones per se and for measuring biologic effects of these substances have been made by scientists in these laboratories. These include:

a. Development of an inexpensive test for diagnosing pregnancy in rhesus monkeys. Reagents for performing the test are currently being distributed to scientists who use this primate for research in reproductive biology.

b. Development of a completely specific method for detecting human chorionic gonadotropin, a hormonal indicator of pregnancy, in specimens of human urine. This is the only completely specific test for this hormone now in existence and supersedes the method developed in these laboratories in 1974 for detecting the hormone in blood and non-specific methods reported from the laboratories. Collecting urine specimens is more convenient, less discomforting, and less expensive than collecting blood samples.

c. Development of a test tube method for measuring the binding of hormones to their receptors in target cells, and measuring the biological activities of hormones that stimulate ovary and testis. These methods make it possible to study such diverse problems as hormone target cell interactions during growth and development, structural features required for interactions of hormones in target cells, and effects of drugs on these interactions. The importance of these assays for practical application in the development of new methods for fertility control cannot be overemphasized.

Maternal and child health - The most significant developments in the intramural program in this area in 1975 relate to the completion of new facilities for in- and out-patient clinical services and some supporting laboratories. Additional scientists and support personnel were added to the Pregnancy Research Branch, anticipating completion of the clinical facilities and the admission of patients. A Neonatal and Pediatric Medicine Branch was organized, a limited number of investigators and support personnel were recruited and research was begun.

Achievement of objectives in perinatal biology will require research into diseases and disorders that threaten the health of pregnant women and their infants and children. In addition, medical, biological, biochemical, sociological, psychiatric, behavioral, physiological, and pharmacological skills are required

for the performance of the necessary studies. Both laboratory and clinical studies currently underway could result in prevention or more effective treatment of Hyaline membrane disease, a respiratory disorder that affects 40,000 premature infants of whom 12,000 die and 8,000 suffer irreversible brain damage each year.

In the area of developmental pharmacology and developmental genetics, scientists are testing potentially feasible methods for identifying persons with genetic predisposition to noxious effects of drugs and other substances that adversely affect the developing fetus and newborn infant. Identifying such persons is an important element in preventing birth defects and adverse drug reactions in mothers, infants, and children.

Studies in an animal model system have shown differences in the regulation of blood sugar levels in neonatal and adult animals. In the neonate, it was noted that milk sugar plays a role in this process, and this simple substance will be used in attempts to successfully treat hypoglycemia, a serious disease state related to and in many cases leading to diabetes, of the newborn infant.

Biometry and Epidemiology:

In 1975 investigations concerning the impact of nutritionally oriented prenatal care programs on pregnancy outcome were completed. Previous studies on lead in formula diets were extended to lead content in blood samples in young children as a function of their diet. Studies on sleep physiology in infancy and the relation of such physiologic patterns to the incidence of sudden infant death syndrome continued. Likewise, twin studies to separate the roles of environmental agents, as opposed to genetic ones, on neurophysiologic variables that may contribute to the incidence of sudden infant death syndrome, progressed further.

At the close of the year the biometry effort brought to near completion the analysis of the possible risks observable in the newborn associated with amniocentesis, a diagnostic procedure used in early pregnancy. A collaborative study on the use of phototherapy in infants with excess levels of bilirubin was continued, and was more than halfway through to accumulation of the two thousand babies required for analysis. Yet another clinical trial was begun on a new treatment of cystinosis, a rare but serious disease in children. Scientists continued to develop a national reporting system for detection of epidemics of congenital malformations in the newborn accompanied by a system to determine their cause. A new statistical procedure was developed to relate several risk factors with the disease to which they are linked so that physicians could predict one's risk of disease from knowledge of the characteristics of the individual. Applications were made to the etiology of stroke in women.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Title IV, Parts E and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	170	$3,884,000	167	$4,007,000	-3	+$123,000
Other expenses.....	--	3,386,000	--	3,311,000	--	-75,000
Total.....	170	7,270,000	167	7,318,000	-3	+48,000

This activity provides for the overall administration, direction, and coordination of the Institute's programs. It encompasses 1) the Director and his immediate staff concerned with administrative management, program planning and evaluation, and research information; 2) the scientific and administrative staff responsible for grant and contract programming, review and administration; and 3) the scientific staff associated with the Center for Population Research, and the Center for Research for Mothers and Children.

Program Direction - This activity provides assistance and counsel to the Director in the fields of management, financial planning, program and statistical evaluation, and analysis in the furtherance of the Institute's programs. During 1976, this activity will continue to provide the necessary professional leadership and technical guidance.

Center for Research for Mothers and Children - This activity provides the necessary professional and technical guidance for the processing and scientific monitoring of the Institute's grant and contract programs relating to child health. During 1975, approximately 971 grants, totalling $58,095,000 will be awarded. In addition, $4,250,000 in research contracts will be awarded.

In 1976, this activity will continue to provide the required technical guidance in the furtherance of the Institute's grant and contract programs in child health. During this period approximately 721 grants will be awarded totalling $45,413,000. In addition, $4,181,000 in research contracts will be awarded.

Center for Population Research - This activity provides the necessary direction, review and scientific monitoring of the grant and research contract programs in the broad spectrum of population research encompassing biomedical and social sciences. During 1975, approximately 552 grants totalling $30,246,000 will be awarded. In addition, $14,793,000 in research contracts will be awarded. In 1976, the Center for Population Research will continue to provide the scientific and administrative support for the grant and contract programs of population research. During this period approximately 380 grants totalling $22,119,000 will be awarded. In addition, $14,004,000 in research contracts will be awarded.

Program Services - This activity provides the necessary administrative management, negotiation, processing, and analysis of all of the Institute's grants and contracts. During 1975, 1,523 grants will be awarded totalling $88,341,000. In addition, research contracts totalling $19,043,000 will be negotiated and awarded. Several research conferences will be held relating to the Institute's programs. In 1976, Program Services will continue to provide the necessary support for the processing and awarding of research grants and contracts. In 1976, approximately 1,101 grants totalling $67,532,000 will be awarded. In addition, research contracts totalling $18,185,000 will be negotiated and awarded. The Institute plans include the continued support of the research conference program in 1976.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Population (Public Health Service Act, Title IV, Parts E and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$45,039,000	Indefinite	---	$36,123,000

Purpose: Population research encompasses four large and complex undertakings: contraceptive development, contraceptive evaluation, social and behavioral sciences, and fundamental research in reproductive biology.

Explanation: The research program includes the biological, medical, demographic, and behavioral aspects of population dynamics.

Accomplishments in 1975: The contraceptive development program for synthesis and testing of antifertility agents is currently studying the safety and efficacy of estrogens and related compounds. A chemical contraceptive for men underwent clinical trials successfully, and the program expanded these studies in 1975. New drug delivery systems, such as biodegradable polymers and new types of IUDs, are being developed. The possibilities of reversing vasectomies continued to be investigated. Researchers continued the examination of risk factors resulting from the oral contraceptives and vasectomy. The behavioral sciences effort has undertaken several new studies of the factors which influence the selection and use of contraceptive methods. Fundamental research is pursuing the elucidation of the mechanism of hormone action in general, and sex steroid hormone action in particular.

Objectives for 1976: Clinical trials will be initiated in 1976 in a major effort to develop contraceptive agents for men. The possibility will be investigated of improving the safety of present oral contraceptives and the effectiveness of naturally occurring hormones. Synthetic estrogens developed in 1974 and 1975 will be evaluated. Research will continue to provide data on the medical effects of intrauterine devices and vasectomy. Increased attention will be given to research concerning the economic and environmental consequences of population change, and the relationship between the status of women and their fertility. Research in basic reproductive biology will continue on the role of hormones in reproduction, and the mechanism of sperm production.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Child Health (Public Health Service Act, Title IV, Parts E and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$62,345,000	Indefinite	---	$49,594,000

Purpose: The Child Health program encompasses research on the segment of the life span beginning with the moment of conception and extending through the later teenage years. The research also includes maternal health and well-being.

Explanation: Research includes the health of the mother; the effect of her health on the child; and the survival of the child through the hazards of intrauterine life, the birth process, and the adjustments to the new extrauterine environment. The focus then shifts to the study of nutritional, hormonal, social, psychological and other factors relating to the kind of adult the child will become. Research investigations include normal development of children and youth, abnormal development and mental retardation, and infant survival and well-being.

Accomplishments in 1975: The perinatal biology and infant mortality program accomplished research concerning low birth weight, maternal diseases and complications of pregnancy, the psychosocial dynamics of pregnancy, initiation of labor, and the sudden infant death syndrome. Advances in the growth and development program were made in the role of nutrition in physiological and psychological development, understanding of the learning process, development of immunologic competence as a function of age, and social, emotional, and intellectual development. The mental retardation program produced important results in a variety of areas, including antenatal diagnosis, genetics, congenital defects, and treatment of communication disabilities.

Objectives for 1976: Continued emphasis will be given to research on the sudden infant death syndrome, low birth weight, maternal diseases and complications,and congenital malformations in the perinatal biology and infant mortality program. The growth and development program will continue its endeavors in the areas of nutrition, learning disabilities, chronic illness in childhood, and adolescent development. Mental retardation research will proceed in the areas of genetic diseases and disorders, nutrition and mental development, early diagnosis and intervention, and treatment and amelioration.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Intramural, Laboratory and Clinical Research (Public Health Service Act, Title IV, Parts E and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
188	$11,413,000	Indefinite	182	$13,027,000

Purpose: The Intramural, Laboratory and Clinical Research program comprises the Institute's intramural effort, including biometry and epidemiology, in the major program areas of population and reproduction, and maternal and child health.

Explanation: The population and reproduction program includes research in reproductive biology, endocrinology, and ecology. The child health program includes research on maternal-child interactions, nutrition and development, behavioral and neurophysiological research, and biochemical aspects of development.

Accomplishments in 1975. The population and reproduction efforts have provided new methods for detecting and measuring hormones and their effects. These results are significant because hormones, and consequently their control, affect all aspects of human reproduction. Maternal and child health results include: the completion of construction of the new perinatal biology facility, which opens the door for the new perinatal research endeavor; progress in developmental pharmacology and developmental genetics which paves the way to preventing birth defects and adverse drug reactions; and a potentially important discovery concerning the role of milk sugar in the neonate which could result in a successful treatment of hypoglycemia. Biometry and epidemiology accomplishments encompassed the extension of sudden infant death syndrome projects and the development of a new statistical procedure to relate risk factors with diseases such as stroke in women.

Objectives for 1976: In population and reproduction, efforts will continue to be directed toward developing the basic information needed to produce safer and more acceptable methods of family planning. A new test to determine pregnancy and a new method for monitoring fetal health during gestation will be examined further in an attempt to bring them to the point of clinical practice. Maternal and child health research will focus on disorders of pregnancy and diseases which significantly contribute to morbidity and mortality in infants and children. Biometry and epidemiology activities will include the preliminary completion of the amniocentesis study; the initiation of new investigations regarding adolescence; preliminary analyses concerning the effects of phototherapy in infants with bilirubinemia; and an analysis of the relationship between a history of induced abortion and subsequent ectopic pregnancies.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Research Management and Program Services (Public Health Service Act, Title IV, Parts E and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
170	$7,270,000	Indefinite	167	$7,318,000

Purpose: This activity supports: 1) the Director and his immediate staff concerned with administrative management, program planning and evaluation, and research information, 2) the scientific and administrative staff responsible for grant and contract programming, review and administration, 3) the scientific staff associated with the Center for Population Research, and 4) research conferences.

Explanation: This activity provides the funds for salaries and other related operating costs for the overall administration and direction of the programs of the Institute. Funds for the grant and contract programs are provided under the appropriate program.

Accomplishments in 1975: The staff supported by this activity continues to provide administrative management, program guidance and supportive services to the Institute's staff, in the furtherance of the Institute's programs to meet its goals. In 1975, it is estimated that 1,523 grants and 204 research contracts will be awarded. Several research conferences will be held relating to the Institute's programs.

Objectives for 1976: This activity will continue to provide for the coordination, administration, and direction of the Institute's research programs. In 1976, it is estimated that 1,101 grants and 193 research contracts will be funded. The Institute plans to include the continued support of the research conference program in 1976.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Amounts Available for Obligation 1/

	1976 Estimate	Interim Period
Appropriation.....	$106,062,000	$24,449,000
Total obligations.....	106,062,000	24,449,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $45,000; Interim - $10,000.

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Population	---	$ 36,123,000	---	$ 6,038,000
Child health	---	49,594,000	---	12,835,000
Intramural, laboratory and clinical research	182	13,027,000	182	3,618,000
Research management and program services	167	7,318,000	167	1,958,000
Total obligations	349	106,062,000	349	24,449,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	349	349
Full-time equivalent of all other positions	85	85
Average number of all employees	429	429
Personnel compensation:		
Permanent positions	$ 7,111,000	$ 1,800,000
Positions other than permanent	769,000	200,000
Other personnel compensation	154,000	40,000
Subtotal, personnel compensation	8,034,000	2,040,000
Personnel benefits	1,240,000	610,000
Travel and transportation of persons	276,000	78,000
Transportation of things	45,000	20,000
Rent, communications, and utilities	320,000	80,000
Printing and reproduction	200,000	50,000
Other services:		
Project contracts	18,185,000	2,900,000
Payment to NIH management fund	5,594,000	1,399,000
Other	2,896,000	889,000
Supplies and materials	1,250,000	290,000
Equipment	490,000	120,000
Grants, subsides, and contributions	67,532,000	15,973,000
Total obligations by object	106,062,000	24,449,000

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the National Institute of Child Health and Human Development consistent with the 1976 estimates. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of fiscal year 1975 modified by program impact of the fiscal year 1976 estimates.

NATIONAL INSTITUTE ON AGING

WITNESSES

DR. NORMAN KRETCHMER, ACTING DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
JOEL R. HEDETNIEMI, ACTING EXECUTIVE OFFICER, NATIONAL INSTITUTE ON AGING
H. RICHARD MILLER, ACTING FINANCIAL MANAGEMENT OFFICER, NATIONAL INSTITUTE ON AGING
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD J. FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We will continue with the National Institutes of Health. Now we have the National Institute on Aging. This presentation will be made by Dr. Norman Kretchmer, the Acting Director. We have your biographical sketch, my fellow actor, which we will place in the record at this point.

Name: Norman Kretchmer, M.D., Ph.D.
Position: Director, National Institute of Child Health and Human Development.
Birthplace and date: New York, N.Y., January 20, 1923.

Education

Cornell University, 1944, bachelor of science.
University of Minnesota, 1945, master of science.
University of Minnesota, 1947, doctor of philosophy.
State University of New York, College of Medicine, 1952, doctor of medicine.

Experience

Present: Director, NICHD; Acting Director, NIA; clinical professor of pediatrics, Howard University; consultant/lecturer, National Naval Medical Center.
1970——: Visiting professor, University of Lagos, Lagos, Nigeria. Bethesda, Md.
1969–74: Chief, Section of Developmental Medicine, Stanford University; professor pediatrics, Stanford University.
1969–72: Chairman, program in human biology, Stanford University.
1959–69: Professor and executive head, pediatrics, Stanford University.
1958–59: Associate professor of pediatrics, Cornell University.
1956–58: Assistant professor of pediatrics, Cornell University.
1953–56: Assistant professor of biochemistry in pediatrics, Cornell University.
1950–53: Lecturer of biology, Brooklyn College.
1948–52: Fellow and research associate of pathology, Long Island College of Medicine.
1947–48: Assistant professor, pathology and biochemistry, University of Vermont.
1944–47: Teaching assistant, University of Minnesota.

Professional societies

American Academy of Pediatrics (fellow); American Association for Advancement of Science (fellow 1963); American Association for University Professors; American Board of Pediatrics (licentiate 1957); American Chemical Society; American Institute for Biological Sciences; American Pediatric Society; American Society for Biological Chemists; American Society for Clinical Nutrition; American Society for Clinical Investigation (council member 1964–67); American Society for Human Genetics; Association of American Medical Colleges; Chilean Pediatric Society (honorary); Chilean Society of Biology (honorary); Chilean Society of Endocrinology; Czechoslovakian Society of Pediatrics (honorary); Harvey Society; Histochemical Society; International Organization for the Study of Human Development (president 1970–76); International Pediatric Association (standing committee member 1974–77); Italian Pediatric Society (honorary);

Perinatal Research Society; Salt and Water Club; Sigma Xi; Societe Francaise de Pediatrie de Paris; Society for Growth and Development; Society for Pediatric Research (president 1967–68); Western Society for Clinical Research; Western Society for Pediatric Research (president 1966–67).

Publications

Numerous publications in the fields of developmental biochemistry, neonatology, genetics, and pediatrics.

Awards

1973–74: Guggenheim Fellowship in Human Development.
1971: Harold K. Faber Professor of Pediatrics, Stanford University.
1969: Borden Award, American Academy of Pediatrics.
1969: Alumni Medallion for Distinguished Service to American Medicine, College of Medicine, Downstate Medical Center, New York.
1965–66: Commonwealth Fund Fellow, Atomic Energy Laboratory, Saclay, Paris.
1965: Honorary Member Faculty of Medicine, University of Chile.
1965: Alpha Omega Alpha (faculty).
1958: E. Mead Johnson Award for Research in Pediatrics, American Academy of Pediatrics.
1957: Commonwealth Fund Traveling Fellowship, St. Mary's Hospital, London and University of Paris.
1955–56: Henry L. Moses Alumni Prize in Basic Research, Montefiore Hospital.
1952–53: Commonwealth Fund Fellow, Montefiore Hospital.

Name: Joel R. Hedetniemi.

Position: Executive Officer, National Institute of Child Health and Human Development.

Birthplace and date: Washington, D.C., August 23, 1940.

Education: The George Washington University, 1962, B.A., the George Washington University, 1967, M.A.

Experience

Present: Executive Officer, National Institute of Child Health and Human Development.
1969–73: Executive Officer, Division of Allied Health Manpower, Bureau of Health Manpower Education, NIH.
1968–69: Acting Executive Officer, Division of Allied Health Manpower, Bureau of Health Manpower Education, NIH.
1967–68: Program Management Officer, Division of Allied Health Manpower, Bureau of Health Manpower Education, NIH.
1966–67: Administrative Officer, National Institute of Mental Health, NIH.
1965–66: Budget Analyst, National Institute of Mental Health, NIH.
1963–65: Management Analyst, National Institute of Mental Health, NIH.
1962–63: Management Intern, National Institutes of Health.

Name: H. Richard Miller.

Position: Financial Management Officer, National Institute of Child Health and Human Development.

Birthplace and date: Hagerstown, Md., May 3, 1941.

Education: Hagerstown Junior College, 1961, A.A.; Shepherd College, 1964, B.S.; American University.

Experience

Present: Financial Management Officer, National Institute of Child Health and Human Development.
1971–72: Budget Officer, National Cancer Institute.
1971: Assistant Budget Officer, National Cancer Institute.
1969–71; Administrative Officer, Financial Management Office, National Cancer Institute.
1968–69: Administrative Officer, Viral Oncology, Etiology, National Cancer Institute.
1966–68: Administrative Assistant, Etiology, National Cancer Institute.
1965–66: Budget and Fiscal Analyst, Civil Service Commission.

Awards: Superior Performance Award, 1970. Quality Increase, 1974.

Mr. FLOOD. Do you have anyone with you that you would want us to meet?

Dr. KRETCHMER. Mr. Chairman, I would like to introduce Mr. Joel R. Hedetniemi, the Acting Executive Officer; Mr. H. Richard Miller, Acting Financial Management Officer; and Dr. Jerry Solon, Planning Officer, of the National Institute on Aging.

Mr. FLOOD. There may be some reason why you have the acting title of the Institute on Aging. How long has this Institute been in existence?

Dr. KRETCHMER. The Institute was enacted into law on May 31, 1974, and was established administratively on October 7, 1974.

Mr. FLOOD. Doctor, you have a prepared statement. How do you want to handle that?

Dr. KRETCHMER. If I may, I would like to present it, sir.

Mr. FLOOD. All right.

Dr. KRETCHMER. Mr. Chairman and members of the committee, I am pleased to appear today as Acting Director of the recently established National Institute on Aging. I assumed this temporary responsibility in September 1974, after serving as a program and organization adviser to the Director of the National Institutes of Health, and after being appointed Director of the National Institute of Child Health and Human Development, the Institute having major responsibility for aging research activities which will form the basis of the new Institute. I will, of course, relinquish this assignment when a Director for the National Institute on Aging is named.

A search committee was appointed last fall to advise the Director, NIH, in selecting the permanent Director of the Institute. The position was nationally advertised in order to obtain the most highly qualified person from the widest range of applicants.

The committee has completed a review and evaluation of many excellent candidates, and we expect Dr. Lamont-Havers to make an appointment to this important position soon.

The NICHD incorporated research on adult development and aging in its basic concept of the study of the entire lifespan. We are presently arranging the transfer of the extramural research activities administered by the Adult Development and Aging Branch and the Gerontology Research Center intramural program to the National Institute on Aging.

While other Institutes at NIH support varying amounts of research on aging questions as they apply to specific aspects of their categorical research programs, NIA alone will have the responsibility for a unified, concerted approach. NIA will support and conduct biomedical, social, and behavioral research, as well as research training on the aging process and the special problems and needs of the aged. I regard NIA as a reflection of a national determination to extend the productivity of its citizenry, to maintain our health as well as possible in our advancing years, and to insure that the benefits of medical research in aging are available for everyone.

IMPLEMENTATION OF THE NIA

To put the description of the aging research program and budget request in context, an explanation of the status of development of the Institute is useful.

The Research on Aging Act calls for development of a comprehensive plan for a research program on aging for all of the Department of Health, Education, and Welfare; requires attention to training for personnel in the field of health care for the aged; and provides for studies to measure the impact of departmental program in aging.

Because implementation of this act must be carried out in concert with several requirements of the Older Americans Act, the legislation which guides the activities of the Administration on Aging, we have established formal coordination with that agency. In addition, we have formed an interagency committee including all other health agencies of the Department to participate in assignment of the various nonresearch provisions of the act and to assure that all programs concerning the aged and aging are covered, avoiding duplication of effort.

The National Institute on Aging was officially established as the 11th Institute of the National Institutes of Health on October 7, 1974. When the Gerontology Research Center and the Adult Development and Aging Branch are transferred from the NICHD, which will occur imminently, the NIA will be an Institute in the full sense of the word, with its own administrative components and initial supporting staff. Also, the National Advisory Council on Aging has been established and will meet this month and again in June.

RESEARCH ON AGING

Since the comprehensive research plan is not complete, and because the NIA Director must play a key role in shaping the Institute's research scope and direction, it would be premature for me to attempt to describe the entire research program of the NIA. I can, however, identify the major research concerns and emphasis which include the normal aging process, degenerative diseases or health problems specifically related to old age, nutrition, and a whole range of social and behavioral problems.

An understanding of the processes of normal aging in man is an essential first step in the effort to translate new findings into clinically useful methods of therapy. At the Gerontology Research Center, for example, scientists have continued an intensive study of a variety of physiological and psychological functions in a large number of male volunteers ranging in age from 20 to 90 years. This long-term project has provided important information on normal measures, with adjustments for age groups, for a number of diagnostic tests, such as those for diabetes and kidney function.

Investigation of normal aging also includes research at the level of our body cells, as many scientists believe that aging is caused primarily by cellular processes. The most direct route to measures for slowing the rate of human aging appears to be studies of enzymes (which catalyze chemical reactions on which all life depends) and the reproductive capacity of cells.

Body systems that show deterioration with age are receiving special attention. The immune system, for example, is at peak competence in childhood and steadily declines with age. This system protects against infections and cancer, and its decline partly accounts for increased vulnerability of the elderly to such diseases. With better

understanding of immunologic defects, methods of treatment will be possible. Recent findings show that restriction of caloric intake delays the deterioration of the immune system with aging in experimental animals.

One of the most damaging and distressing aging defects is senility. Characterized by loss of recent memory and the ability to handle some kinds of mental tasks, senility renders some persons heavily dependent on families and society. Individual cases probably are due to combinations of various disease processes occurring in some but not all people, and changes occurring in everyone with increasing age. Animal studies of memory loss and changes in the brain, in addition to behavioral studies, are providing leads to prevention or treatment of senility and may add to our understanding of basic aging processes.

The problems that the new National Institute on Aging will face concerning new information in the area of behavioral and social sciences are many. This area of investigation, which is extremely important, must be accomplished with the maintenance of a constant dialog with the research branch of the Administration on Aging. There is no doubt a relationship between the social and behavioral problems faced by the elderly and their ability to maintain an adequate functional state. We need careful studies of ways to serve and support the elderly, to enable them to continue to relate to society, despite physical and psychological changes, as long as possible.

Today, about two-thirds of all Federal health care funds are directed toward persons over age 65. Perhaps 1 million of these people live in institutions, and a significant number of these are incapacitated by age-related diseases. Between now and the end of the century, the U.S. population over age 65 will increase by 50 percent, from about 20 million to 30 million. We have a mandate to learn more about the degenerative processes that begin early in life and result in disabilities in middle and later life, so that they can be better understood, slowed and ameliorated.

CONCLUSION

Mr. Chairman, the 1976 budget request for the National Institute on Aging is $16,190,000. I will be pleased to answer any questions or to provide additional information.

APPOINTMENT OF DIRECTOR

Mr. FLOOD. Doctor, when do you expect a permanent Director to be appointed for this Institute?

Dr. KRETCHMER. If you don't mind, Mr. Chairman, I would like to refer that question to Dr. Lamont-Havers.

Mr. FLOOD. All right.

Dr. LAMONT-HAVERS. To date we have considered a large number of potential candidates for this position. We have offered the post to eight highly qualified individuals, all of whom felt that the salary level which we are offering is far less than their needs. They do not wish to make martyrs of their families. So we are having great difficulty in filling this position from the pool of excellence from which we would like to draw.

To answer the question specifically then, I don't know when we will be able to appoint the Director.

RESEARCH PLAN

Mr. FLOOD. The Research on Aging Act requires that within 1 year after enactment there was to be a research plan designed to coordinate and promote research into many, many fields, biological, medical, psychological, social, emotional, and the economic aspects of aging, all of those things.

When do you expect to have that plan completed?

Dr. KRETCHMER. Mr. Chairman, to expedite implementation of the Research on Aging Act, we first formed an interagency committee to consider not only the research plan, but also aspects of manpower training and information and education programs required in the law.

We have had a preliminary meeting with some of the Members of the National Advisory Council on Aging to indicate the obligation of the Council to participate in preparation of the research plan. The Council will meet next Wednesday and Thursday, in an open meeting, to begin its deliberations on implementation of the act.

Mr. FLOOD. When do you expect to have the plan completed?

Dr. KRETCHMER. We expect to have a plan ready by May 31, 1975.

Mr. FLOOD. When you do, will you send a copy to each member of this committee?

Dr. KRETCHMER. Yes, sir.

TRAINING

Mr. FLOOD. What kind of personnel should we be training in this particular field of health care for the aged?

Dr. KRETCHMER. Mr. Chairman, the Institute was established to conduct and support research on the biomedical and behavorial aspects of the aging process and the special problems of the aged. In terms of health care for the aged, which is your specific question, we should train people in the general area of gerontology and geriatrics.

In addition, I would say that we should consider training allied health personnel.

Mr. FLOOD. You mean paramedics?

Dr. KRETCHMER. Not only paramedics, because in the field of aging more than any other field we are concerned with all the rehabilitation, behavioral, and social aspects of health problems, so allied health personnel would be a better description.

Mr. FLOOD. That is a better term.

Now, is there a shortage at the present time of this type of individual?

Dr. KRETCHMER. While I do not have data at hand today, my impression is that there is a shortage of individuals who are particularly trained in this area. Also, if we make a statistical evaluation of the increasing number of aged and aging people in relation to the numbers of personnel we are training, then there is a shortage.

Mr. FLOOD. How many should we be training on an annual basis?

Dr. KRETCHMER. To give you accurate figures, I would have to supply that for the record.

[The information follows:]

NATIONAL INSTITUTE ON AGING

ALLIED HEALTH MANPOWER—HOW MANY TO TRAIN?

Allied health manpower is defined broadly to include the professional, technical, and supportive workers who complement or supplement the functions of physicians, dentists, and registered nurses. The term is used to include workers in patient care services, administration, teaching, and research, as well as personnel in organized environmental health activities, such as environmental engineers. Although training requirements for the many allied health professions vary, these occupations are frequently divided into two groupings—those for which the basic preparation is at the baccalaureate level, and those for which it is less than baccalaureate. For both categories, the respective level of academic and practical training is designed to produce health personnel who are generalists within their individual disciplines, rather than specialists for different services or consumer groups. Thus, while such allied health personnel as physical therapists, occupational therapists, rehabilitation counselors, and staff of extended care facilities are particularly important to the provision of health care for the elderly, they are not trained, initially, to work only on this field. Further, older people benefit from services of the full range of allied health personnel, as do younger people, in hospitals and a variety of other medical and dental care settings.

Consideration of training needs, then, must be addressed in terms of all allied health workers rather than only those identified with health care for the elderly.

Statistical concerns

The need for reliable statistical data on manpower in the allied health field is great. However, due to the large and rapidly growing numbers and types of workers in this field and the inadequate data base, the assessment of current and future supply is extremely difficult. Some of the problems in establishing reliable data have been:

1. Lack of definition of the many allied health professions and occupations;
2. Lack of reliable estimates of current and past supply of these workers;
3. Limited information on the characteristics of these workers;
4. Limited knowledge about the impact of task delegation on future supply estimates.

Perhaps the most important lack is an objective against which to measure our ability to provide health services. Forecasts of requirements for manpower must be based on manpower utilization, and utilization is related more to rising standards of medical care than to simple growth in population or volume of health services.

The result has been, unfortunately, that accurate estimates of needs for allied health manpower are not available.

Trends in allied health education

Recent studies sponsored by the Bureau of Health Resources Development, of the Health Resources Administration, indicate that the number of collegiate programs in allied health education has increased rapidly over the past several years—from approximately 1,300 in 1965 to over 5,100 in 1974—with a concomitant increase in graduates—from almost 11,000 per year to over 51,000. These data appear to show that, even though the changes are due in part to amalgamations with noncollegiate programs, the principal factor affecting trends for the allied health workforce will no longer be the numbers who need to be trained but quality standards for the work force.

For the basic statistical data that would allow us to judge the numerical adequacy of our manpower supply, we will need periodic national surveys covering employment and requirements in hospitals, extended care facilities, and other employers, as well as educational program surveys and efforts to distinguish between allied health workers who have recognized credentials and those who do not.

Mr. FLOOD. How many will you be able to train under this budget you are talking about?

Dr. KRETCHMER. The requested budget would provide for 45 fellowships, in addition to approximately another 76 full-time equivalent trainees under 18 training grants. So the total that we would be training would be on the order of about 120.

Dr. LAMONT-HAVERS. The training which Dr. Kretchmer describes is for research personnel only, and not for the preparation of health professionals who deliver health services. The Institute does not have the authority to train health care personnel.

Dr. KRETCHMER. The training programs for allied health professionals would be under the auspices of the Administration on Aging and the Health Resources Administration.

COORDINATION OF RESEARCH

Mr. FLOOD. In your opening statement you said you had established "formal coordination" with the Administration on Aging. What do you mean by "formal coordination"?

Dr. KRETCHMER. By "formal coordination" I mean that we have, through memoranda signed by the Secretary, established an interagency committee including the Administration on Aging, Health Resources Administration, Health Services Administration, National Institute of Mental Health, Veterans' Administration, and a representative of the Office of the Assistant Secretary for Health. It is really a formal-informal relationship with the Administration on Aging. I keep in constant contact with the Commissioner, Dr. Flemming, and his staff, and serve ex-officio on the National Advisory Council on Aging. Also, the Administration on Aging is represented on the search committee for the Director of NIA.

SENILE DEMENTIA

Mr. FLOOD. In your justifications you state: "One million persons over 65 live in institutions and a significant portion are incapacitated by senile dementia." What do you know about that problem?

Dr. KRETCHMER. I would like to differentiate between senility and senile dementia. Senility is defined as an inability to remember recent events and to handle some kinds of mental tasks. Senility also involves degenerative processes and feebleness.

Senile dementia is another extreme. It could really be classified under the term "psychosis." The problem here is a lack of relationship to reality. Whether senility leads to senile dementia or not is still an open question.

Mr. FLOOD. What research will you be doing this next year in this budget which will get at the root because of this problem of senile dementia? In other words, if you could prevent or treat that kind of senility you would be saving a lot of money as well as improving vastly the quality of life of a lot of people.

Dr. KRETCHMER. I think it is a very serious problem. We are doing research in this area.

For example, we have found out that cellular and vascular degeneration, particularly in various parts of the brain, are a basis for senility. One can set up animal models to study this type of a problem. So what

we are headed for in our research activities is just what you have pointed to, Mr. Chairman. We are headed for an understanding of the mechanism of the development of senility and eventually senile dementia, if you will, so we can prevent or alleviate these problems.

We also have research in the social and behavioral sciences which would impact upon the whole problem of senility. We have found out through sociological research that older people become depressed when you shift them geographically. We might say that this conclusion seems logical, but it is also a scientific fact.

Mr. FLOOD. You may want to develop the extent of your research for the record. You may want to say more about this as to the extent of what your program could or will be this next year.

[The information follows:]

SENILE DEMENTIA RESEARCH

From research investments of the National Institute of Child Health and Human Development, several important leads have emerged regarding senile dementia, and thus will be pursued by the National Institute on Aging in 1976. For example, there is a loss of synaptic contacts between brain cells, and also a loss of neurons, both in normal and senile aging. These factors suggest a relationship to loss of brain function and of mental capacity. A brain antibody appears in the blood serum which may have cytotoxic effects, perhaps explaining in part the decrease of neurons. Abnormalities of proteins develop in the tubules within nerve cells that become twisted and packed, known as neural-fibulary tangles, and also in soluble proteins of the brain. Extracellular amyloid plaques and high levels of aluminum appear in the senile brain. These changes of proteins as well as the accumulation of aluminum may directly affect brain function.

The extent to which this effort will be developed depends heavily on the availability of new resources or the realinement of existing resources under the National Institute on Aging's research plan, which will be promulgated in the near future. At this time, it is considered possible to double the research effort from approximately $200,000 in 1975 to $400,000 in 1976. New initiative areas would include: biochemical correlates of aging in the brain, biofeedback and behavioral changes throughout life, and drug effects as related to physiology and behavior.

LONGITUDINAL STUDY

Mr. FLOOD. On page 125 of the justifications you say: "The year 1975 will see the completion of the eighth 2-year cycle of testing on the Longitudinal Study of Human Aging." Can you tell us what you have learned from these studies?

Dr. KRETCHMER. Yes. This study has been going on for 16 years.

Mr. FLOOD. How have these studies helped the average citizens, the taxpayers, in this country?

Dr. KRETCHMER. The results of this study have helped the taxpayer because an understanding has been gained of what goes on during the aging of men.

Mr. FLOOD. It is the completion of the eighth 2-year cycle.

Dr. KRETCHMER. Yes, sir.

For example, the investigators have been looking at the control of blood sugar and the disposition of drugs in people as they age. They have found some very interesting things, habits change as people get older, that they drink less alcohol, smoke less, and drink less coffee. It is the relationship of the habitual use of caffein, nicotine, and alcohol that affects the distribution of drugs in the bloodstream. To

put this into practical terms, these data lead to the fact that if you give an older individual the same dosage of a drug as you would to a younger individual, then the result is much more drastic. If I remember the earlier testimony, this particular finding was in relation to Valium.

Mr. FLOOD. Yes. We were concerned about the publicity about the nursing homes and oversedation of patients there. Is it actually oversedation or merely the condition you are talking about, young people and older people given the same amount of Valium.

Dr. KRETCHMER. The latter, with the more drastic effect in the older person.

This is the type of information that has come out of the longitudinal study of the males. I think we can see a very ready application in the sense that the dosage of drugs used in the older people should be cut down to equal their lower metabolic rate. I would like to insert a special report on our aging program.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT,
NATIONAL INSTITUTES OF HEALTH

The number of persons 65 years old and over has sharply increased over the years since 1900. The percentage of people over 65 years in the population has increased from about 4% to approximately 10%. In 1900 the average lifespan for a person in this country was 49 years; today it is 71 years. Primarily responsible for this increased life expectancy has been a decrease in mortality from infectious diseases.

Today there are more people in the population 65 years of age and older than there has ever been in the history of this country. Consequently there has been an increasing awareness of the deterioration in biological, psychological and social processes with age. Scientists are striving to learn more about the changes that accompany aging in an effort to exert greater control over these deteriorative changes. These are the concerns of the National Institute of Child Health and Human Development as the Federal agency with primary responsibility for supporting research on aging. The aim of this research is to provide information that will make it possible for the elderly to live healthier and more well-adjusted lives. Such improvement in health can be expected to lead to a longer average lifespan.

The Institute in addition to supporting research in universities, medical schools and other research institutions around the country through the award of research grants also has staff scientists who conduct research at its intramural Gerontology Research Center in Baltimore. An extramural program of research grants in aging is supported by the Adult Development and Aging Branch of the Institute.

On May 31, 1974 the President signed legislation which provides for the establishment of a National Institute on Aging. The National Institute on Aging has been established at NIH although it is not fully operational at present. When it becomes operational the NICHD programs in aging (the Adult Development and Aging Branch and the Gerontology Research Center) will be transferred to it.

1. THE EXTRAMURAL PROGRAM ON AGING RESEARCH

The Institute has identified certain areas of research on aging as areas of special need or that hold special promise. These areas of research compete equally for available funds, however. Several of these areas are described below.

a. Biomedical Aging

During development and after maturation various deleterious changes occur in the human body. Because the body does not possess the abilities to repair all these changes, some accumulate and result in the progressive deterioration called aging. At present medical intervention can compensate for a small part of aging damage. One of the major aims of biomedical research is to make more extensive compensation possible. For example, intervention is already possible in the treatment of the menopause, the condition that results from ovarian aging. Probably in the future, physicians will be able to intervene more vigorously than now in the severe immunological deficiencies of the elderly. An understanding of the basic processes of cellular aging may open a number of therapeutic possibilities. Research in these areas: the menopause, immunological aging, and the cellular basis of aging is discussed below.

1) The Menopause. The variation in ovarian production of estrogens over the lifespan is remarkable. Estrogen production increases dramatically at puberty and declines drastically at the time of the menopause. Between puberty and menopause a gradual deterioration of ovarian structure occurs and is responsible for the diminished output of estrogens. The decline in estrogen output is clearly associated with hot flashes and genital atrophy. Indeed these changes can be reversed by the oral administration of estrogenic substances.

Some physicians suspect that some other deteriorative changes such as rarefaction of bone and arteriosclerosis may be due to the ovarian failure that causes the menopause. However, a causative relationship between ovarian failure and those diseases has not been definitely established.

Although it is clear that estrogen therapy of the menopausal and postmenopausal woman has beneficial effects, it is possibly not without risk. In view of firm data on increased thromboembolic disease in women on oral contraceptives, the risks and benefits of replacement therapy need careful examination, particularly since it is estimated that 13% of postmenopausal women are currently taking some type of intermittent replacement therapy.

The menopause, its sequelae and treatment have major public health implications, since it affects the health and well-being of a major segment of the population. Studies on the mechanism triggering ovarian involution, estrogen sources and production, as well as studies on the risks and benefits of sex steroids are needed to understand the menopause and its relationship to aging processes and degenerative diseases.

The Institute supports research on sources of estrogens other than the ovary in postmenopausal women. The Institute funds by contract a retrospective study of the effects of estrogen therapy on the occurrence of stroke and hypertension. Also, grant supported studies are currently underway that are aimed at acquiring information and data on understanding the mechanisms involved in ovarian involution.

2) Immunological Changes. Immunology emerges today as an important area for the study of aging because the changes that occur in immunologic competence with age underlie the increased susceptibility of the elderly to infectious diseases. The importance of the immune system as a defense against infectious diseases has long been known. While the young remain healthy because of a highly efficient immune system the elderly with their declining immune response are particularly susceptible to infectious diseases. It is also recognized that immunologic competence may play an important role in preventing the development of cancer and autoimmune diseases.

Fuller understanding of the nature of the deterioration with aging will permit design and application of measures to beneficially modify immunity. At our stage of progress primary emphasis must be directed at defining the immunologic deficiencies of the aged at the cellular and molecular level. The development of new means to augment immune competence in the later years of life would represent a major advance in improving the health of older people.

3) Cellular Aging. Although complex systems such as the endocrine and immune systems may be modified to control some aging manifestations, more vigorous intervention might be possible if the cellular and subcellular aging processes damaging these systems were understood. Little is known about

cellular and subcellular aging. The progress of modern biology has, however, provided methodology and concepts to investigate the processes involved. Because cellular aging underlies much of what is manifested in the aged, the Institute places special emphasis on this area of research.

Through tissue culture and transplantation studies, scientists have learned that normal mammalian cells cannot reproduce themselves indefinitely. This fact has caused a profound change in theories of aging by emphasizing that an understanding of organismic aging may have to be based on cell biology.

The cell whose limited ability to reproduce itself has been most intensively studied to date is the fibroblast. This cell, which is similar to most dividing cells within the body, may provide a model for them and at the same time has its own importance as a producer of collagen and mucopolysaccharides. These substances form the structures which give mechanics to the cells of the human body. The Institute is supporting research on many aspects of the limited reproductive potential of fibroblasts, for example, membrane, mitrochondrial, and lysosomal function, protein and nucleic acid metabolism, peroxidation reactions, and hormonal responsiveness. Further, considerable effort is currently being directed to an expansion of this program to include more cell types representative of a variety of human aging phenomena. It is hoped that these and other studies will disclose the mechanisms by which cell reproduction potential and other functions are limited and the consequences of such limitations or the effects leading to them. Such discoveries will be particularly important if they can be generalized to other cells and tissues within the body.

b. Mental Aging

Decline in intellectual ability with age is of great interest to the Institute and is becoming of increasing concern in a society which has increasing numbers of older people.

Current knowledge of changes in the higher mental processes during the adult years has been based mainly on comparisons between young and old persons. Since the younger persons probably have better educational backgrounds the test results are likely to be biased in favor of the young. However, the results of such studies strongly suggest that there is deterioration in mental function with age. This deterioration is much more severe in non-verbal than in verbal abilities. The mechanism of this change is not known. However, it is thought that it may be related to the progressive loss of brain cells that occurs with age. The decline in mental function just described does not incapacitate an individual and can only be detected by special tests.

However, other more serious impairments of mental function may occur with aging. For many years, the severe cases of mental deterioration in the elderly were attributed to vascular disease. There is increasing evidence that this is not usually the case, and that, in fact, most instances of senile dementia are due to changes in the brain cells produced by some unknown mechanism. The Institute is supporting studies aimed at determining and ameliorating these changes.

There is interest in research aimed at determining which changes or degree of change in mental functioning as measured by intelligence tests and tests of cognitive ability can be attributed to age and what changes to some other

factor or factors. Much of the research on change in mental function has been complicated by the intermingling of several factors. For example, there are cohort differences and there are age differences which until relatively recently were not distinguished.

c. Social Aspects of Aging

The average lifespan has changed tremendously since the evolutionary emergence of mankind and there have been concomitant changes in the age-structure of the many different populations that have populated the earth. There is no reason to think that the population age-structure will not continue to change and it is conceivable that there will be major changes in the average length of life.

Basic to the process of planning for the health, social and economic welfare of the older population is an adequate understanding of its future size and composition. How this country's population size and age-structure develop in the coming years will be determined primarily by its future fertility and mortality rates. There is a growing need for appraising the impact of potential medical control programs in affecting morbidity and mortality levels for specific diseases and causes of death. There is increasing importance of mortality as a factor influencing population change especially under conditions of lower fertility rates and movement towards a stabilized population. In connection with these concerns for the demographic aspects of aging populations the Institute is supporting a survey of existing population models with an eye toward suggesting more rigorous and realistic methods of forecasting mortality trends.

2. INTRAMURAL RESEARCH

The Gerontology Research Center (GRC) remains the focal point for research on the aging processes within the National Institute of Child Health and Human Development and the NIH.

The 154 scientists, technicians and supporting staff of the Center study the physiological, biomedical and behavioral aspects of aging in both humans and a number of animal species. Their overall goal continues to be directed toward gathering fundamental knowledge of aging that can be used effectively by physicians, other professionals, and the public to enhance the quality of life for all older people.

The Baltimore Center, in addition to its own programs, houses a guest scientist contingent with more than 50 non-government personnel working on projects related to aging, or the illnesses that afflict older people most frequently. Research advances this year at the GRC follow.

a. Learning Body Control

One of the most depressing and debilitating infirmities of the elderly is the loss of control over excretory functions. Such losses cause considerable hardship for the family caring for an older person, and often this disability forces the family to place the patient in a nursing home.

A clinical research project of the Laboratory of Behavioral Sciences, in collaboration with physicians from Baltimore City Hospitals, proved that some patients can learn voluntary control over their excretory functions. This held true for patients ranging in age from six to 60 years. Some of the patients had suffered severe soiling problems for as long as eight years, and all of them had a history of organic disease which underlay the incontinence.

The technique involves operant conditioning (training by reinforcing correct behavior) and feedback to the patient. In these studies the patients were taught to control a specific reflex response of their bowel by watching a needle trace that response, and by being instructed (reinforced) in the correct nature of that response. Such learning is rapid, and complete training in all cases was accomplished in four or fewer training sessions.

Further applications for this treatment now are being tested in additional incontinent patients and in persons suffering other lower digestive tract disorders.

b. Teaching the Elderly

One of the most durable adages about older animals and people is that "you can't teach an old dog new tricks". However, animal experiments by an investigator in the Laboratory of Behavioral Sciences show it is possible to teach old rats tasks which they were unable to perform previously.

An old animal has trouble learning its way through a complicated maze because it tends to make the same error again and again, something a young animal seldom does. That is, it returns to the same alleys (deadends) in the maze even though previous experience should have taught it to avoid such an error. In the GRC study, training designed to prevent initial errors helped the old failures become efficient performers.

Therefore, it should be possible for older people to learn new tasks by designing learning situations which prevent errors during initial training.

c. Drug Metabolism in Adults

The effect of aging on the body's ability to distribute and metabolize drugs has received scant attention in the past. Therefore, the Baltimore Longitudinal Aging Study offers a unique opportunity to study such effects. This long-term study involves some 650 community-dwelling men, aged 20-96 years, who visit the Gerontology Research Center periodically to take numerous tests measuring age changes.

Scientists in the Clinical Physiology Branch selected two drugs, both metabolized by the liver, but by different mechanisms, to assess age changes. Alcohol was chosen because of its widespread use, its physiological effects, and the profound clinical, legal, and social problems involved in its use. The other drug, antipyrine, was picked because it represents a drug family metabolized by another basic liver mechanism.

Both drugs were given intravenously to volunteers whose chronological ages covered the adult life span. The study shows that alcohol is metabolized as well by older men as it is by younger men.

On the other hand, the ability to dispose of antipyrine decreased with age. An analysis of data on smoking and coffee or tea drinking habits, collected routinely on members of the longitudinal group, suggests a possible reason for the slower metabolism of antipyrine in older men. Both habits, regardless of age, speed up antipyrine metabolism. However, cigarette smoking and coffee or tea drinking declines in older volunteers. This indicates that much of what appears to be a decrement related to biological aging may be attributed more to age-associated changes in habits.

d. Age and Standards of Normality

Clinical scientists are becoming more and more interested in the concept of "normality" as it relates to treatment of aged patients. The identification of disease and classification of its severity depends on accurate age-corrected standards of what is normal.

Recently, such standards became available for the 24-hour creatinine clearance test which is a measure of kidney function widely used for clinical diagnosis. Studies in the Baltimore Longitudinal Aging Study reveal that the change in creatinine clearance with age is progressive and becomes evident even in the early adult years. The data clearly demonstrate that these age changes are not secondary to the increasing prevalence of kidney disease with aging but are due to true biological aging.

From these data, a nomogram has been developed by Clinical Physiology Branch investigators which allows the physician to compute easily the rank or score for each patient as compared to that of normal subjects of the same age. Use of this nomogram should help improve clinical diagnosis and treatment of kidney ailments in older patients.

e. Obesity Measures

Obesity is a known high risk factor in the development of coronary heart disease, diabetes and other diseases as well as being a predictor of mortality. Accurate assessment of obesity in large numbers of people is extremely difficult. Height and weight tables are useful but limited because they fail to separate increased weight due to fatness from that due to muscularity.

Measurements of body composition have been taken for the past 15 years in Baltimore Longitudinal Aging Study subjects examined every one to two years. Since both weight gains and losses occurred in these men as they aged, various indices of obesity can be related to weight changes. The nature of the study itself made it possible to test the accuracy of measures used to indicate obesity. Two methods widely used to augment height/weight data were tested. One measures body circumference, abdominal girth for example, and the other estimates layers of fat under the skin using pinch calipers.

The experience of these studies shows that lower abdominal circumference is far superior to skinfold measures as an indicator of fatness. Furthermore, changes in girth effectively reflect weight changes in young, middle-aged and old adults. The use of this measurement should greatly improve evaluation in programs directed toward improving the health status of the aged.

f. Hormonal Response in the Old

One fairly common manifestation of aging is a general decrease in the body's ability to respond to various stimuli. One reason for this is the older organism's reduced capacity to make the correct biological response to hormones, in particular those from the pituitary and adrenal glands. Initiation of these responses requires the binding (attachment) of hormones to specific target sites of various tissues.

Animal studies carried out in the Clinical Physiology Branch show that these crucial hormone receptor sites are partially lost during aging. This helps to explain some of the reduced responses to certain hormones known to occur in aging animals and humans.

g. Aging Effects on the Heart

The ability of the heart to contract optimally and to respond to exercise and to other life stresses has been shown to diminish in both experimental animals and man with advancing age. The mechanisms underlying this aging effect are now being studied in heart muscle preparations of old and young rats.

These studies by the Clinical Physiology Branch show that the tension developed with each beat is unaffected by age, but the time required to generate this tension is significantly prolonged in the aged heart. The mechanism of this prolonged contraction appears to be related to abnormalities in the active heart relaxing system, namely, a delay in the removal of calcium from contractile elements. Furthermore, the response to stress, elicited by exposure of the heart muscle to adrenalin is significantly diminished in the aged heart.

These results suggest mechanisms which may explain age-associated changes in the cardiovascular system. An understanding of these mechanisms would prove extremely useful in the diagnosis and therapy of older cardiac patients.

h. The Aging Immune System

Past studies by investigators in the Laboratory of Cellular and Comparative Physiology revealed that the loss of normal immunity that accompanies aging results, mainly, from changes in the body's own immune cells. This is reflected in their lessened ability to reproduce themselves and become efficient disease fighters. Thus, the older person becomes highly susceptible to diseases which are effectively controlled by the immune system in younger people.

This year, these investigators found one possible way to bolster immunity in the old. Thymic and bone marrow tissues taken from young animals and transferred to old mice led to restimulation of the immune system in the old animals. This indicates that the immune system in the old can be strengthened although transplanting young cells may not be the best method to use. The GRC scientists are searching for a number of other ways to improve the efficiency of the immune system in older people.

i. Cellular Aging

A decline in cellular proliferation of certain tissues is an important feature of human aging. An understanding of the molecular mechanism is crucial, for it will contribute to our knowledge of human aging at the cellular level.

Researchers in the Laboratory of Cellular and Comparative Physiology examine cultured human fibroblast cells which have a diminished ability to divide as they age. They have found a generalized increase in these cells' large molecules, such as proteins and ribonucleic acid, which are necessary for maintenance of cellular integrity. Further studies are aimed at delineating the relationship between age-related cellular accumulation of large molecules and cellular replication.

j. Age and Impaired Cell Communication

All cells depend on the efficient communication of genetic information for their survival. In other words, messages must be sent from genetic headquarters (the nucleus) to the living area of the cell (the cytoplasm) to trigger production of proteins needed to maintain cell life.

Metal ions (trace metals) in small amounts are necessary for the effective transmittal of these genetic messages. However, earlier studies in the Laboratory of Molecular Aging showed that metal ions present in excessive amounts produce errors in the transfer of genetic messages. Furthermore, studies of human cells in tissue culture show that the concentration of metal ions rises markedly with age.

These investigators have now found evidence suggesting that one way ions contribute to deterioration of cell genetic information is by shortening message units sent from the nucleus to the cytoplasm.

CALORIC RESTRICTIONS

Mr. FLOOD. Now, again in your budget justification you state: "Recently it was found that caloric restriction delayed the deterioration of the immune system that occurred with aging."

Suppose you explain that a little more fully and tell us what are the implications of that finding?

Dr. KRETCHMER. Mr. Chairman, the effect of caloric restriction upon a number of diseases has been known for a number of years. When I was a graduate student at the University of Minnesota, there were many experiments done on the relation between caloric restrictions and the incidence of cancer in mice. The animals which were semi-starved did not develop cancer in as large numbers as those fully fed. This means that, if you are skinny, you are probably healthier in terms of immune responses and development of a variety of other mechanisms for handling disease than if you consume too many calories.

Mr. FLOOD. How have you provided that information to the providers of health care?

Dr. KRETCHMER. Information dissemination is handled through scientific publications, conferences, pamphlets, and open symposia. There are presentations at the American Medical Association and in periodicals such as the Journal of the AMA and the media of the societies for gerontology and geriatrics.

Mr. FLOOD. Your budget calls for a total investment of $16,190,000 in this aging research.

In your professional judgment, how much is needed annually to adequately research this problem of aging? Do you have any figure?

Dr. KRETCHMER. I would say that approximately twice that amount would be needed for 1976. That is my professional judgment.

COORDINATION OF RESEARCH

Mr. FLOOD. It seems to me that the Aging Institute and the Institute on Child Health and Human Development will have to be pretty closely coordinated in their activities. How can you accomplish such a coordination, and do you plan that?

Dr. KRETCHMER. Yes, sir. This is a subject that has concerned me greatly. I hope to be relieved of the post of Acting Director of the National Institute on Aging as soon as possible. I will carry through as Acting Director until the end of this fiscal year. I am concerned that both Institutes conduct and support research on problems of human development, and that some of the answers on aging are going to come from studies of infancy and childhood. I don't quite know how to insure that there can be constant coordination and cooperation between programs.

I would prefer, Mr. Chairman, to think about this operating problem and to respond with a plan. I wish I had one at the moment.

Mr. FLOOD. All right, I can understand that. Suppose you do that, though. I would like to see something in the nature of a plan, your plan.

Dr. KRETCHMER. As soon as the plan for coordination is completed, a copy will be submitted to the committee.

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Mr. FLOOD. Mr. Michel.

FUNDING OF HEALTH CARE FOR ELDERLY

Mr. MICHEL. Doctor, first of all, maybe this ties in the last question of the chairman. I notice in your testimony you say today about two-thirds of all Federal health care funds are directed toward persons over the age of 65. Now if I am trying to hold things pretty tight in the budget, my natural reaction would be to say, well now, Doctor, if all that amount of money is already going to persons 65 and over, what are we doing putting more money into your Institute? I think I might know what kind of response you have, but I would be curious to know.

Dr. KRETCHMER. Surely. The statement says two-thirds of the health care moneys are going into aging, but not that two-thirds of the moneys are going into research. The budget of this Institute is only for research and does not attend to the many other special problems and needs of the elderly and the aging.

Mr. MICHEL. I thought maybe the response might have been that you would hope with the kind of money you get in your Institute that sometime yet in our lifetime two-thirds of all Federal health care funds would not have to go to that segment of the population, but maybe that is being a little optimistic.

Dr. KRETCHMER. No; Mr. Michel. I have spent a whole lifetime in research and I must say I have balanced it with delivery of health care. My experience over 25 years in medicine has been that, as research opportunities permit themselves to be applied, inevitably we save money.

The examples I can give you have to be from my own field. If we take a look at the problems of German measles or polio in this Nation we have saved a good deal of money. If we could, through the National Institute on Aging, accomplish some of our optimistic goals, we surely could reduce the amount of money expended such as for senility, the problem Mr. Flood referred to earlier.

ESTABLISHMENT OF NEW INSTITUTE

Mr. MICHEL. I note in the item of transportation you have an increase from $24,000 to $50,000. Does this relate to your move or does it involve something else?

Dr. KRETCHMER. Mr. Hedetniemi will answer.

Mr. HEDETNIEMI. This is an estimated amount to cover moving expenses of new senior staff that we hope to hire for the Institute.

Mr. MICHEL. Will that transfer to the new Institute of Gerontology Research Center be completed by the beginning of the new fiscal year?

Dr. KRETCHMER. Yes. The Gerontology Research Center will remain in Baltimore as the intramural program of the NIA. The Director's Office and supporting staff will be located at the National Institutes of Health in Bethesda.

Mr. MICHEL. I am not sure what your response was with respect to the chairman's question regarding the comprehensive research plan and when it was to be ready.

Dr. KRETCHMER. By law, the comprehensive research plan must be ready by May 31, 1975.

Mr. MICHEL. Will that be met?

Dr. KRETCHMER. Yes, sir.

Mr. MICHEL. Then we would not be anticipating the holding up of funding of new research contracts for any reason?

Dr. KRETCHMER. No. We now have a National Advisory Council on Aging. They are meeting next week to work on the research plan for the National Institute on Aging.

RESEARCH GRANTS

Mr. MICHEL. Would you define for me the difference between your competing and noncompeting research grants?

Dr. KRETCHMER. Yes. The noncompeting research grants are those research grants in their second or later years which had been approved for 2 to 5 years. There are moral obligations to fund those grants each year on the basis of meritorious work accomplished the year before. They do not go through a competitive merit review each year.

The competing research grants result from either brand new applications in a given year or from applications to renew long-term approval of a project whose initial commitment period has been completed. Those competing research grants go through the entire peer review process of the NIH, are assigned priority numbers, and are funded if sufficient funds are available.

Mr. MICHEL. In that noncompeting area, where they do run 3 to 5 years, is there no review process at all? There is some, isn't there?

Dr. KRETCHMER. Yes. We do have review, as a progress report is required every year. This report is studied by the Institute staff to see whether the investigator has fulfilled what he said he would do, as well as whether he or she was productive during that year. For certain larger grants, which were given for 5 years, there will also be a site visit, usually around the third year. So, there is constant monitoring or review of the research grants.

Mr. MICHEL. How many research grants are actually being completed this year?

Dr. KRETCHMER. In the National Institute on Aging?

Mr. MICHEL. Yes.

Dr. KRETCHMER. I will ask Mr. Miller.

Mr. MILLER. There are approximately 12 noncompeting grants that will be completed this year.

Mr. MICHEL. Now I won't ask you right off the top of your head, Doctor, but for the record, will you give us a little exposition in the record of what we accomplished, what we realized and what we learned from those that have been completed?

Dr. KRETCHMER. Yes, sir. We will supply that for the record.

[The information follows:]

ACCOMPLISHMENTS FROM COMPLETED GRANTS

There have been numerous accomplishments from the 12 noncompeting regular research grants that are being completed in 1976. A brief summary of these significant findings follows. Many of these grants are studies of portions of the fundamental aging process, at the cell and organism level, including the functions of various substances, and the effect of aging on these cells and substances.

1. Dr. David E. Comings, City of Hope National Medical Center, Duarte, Calif.—This study examined cytoplasmic DNA-binding proteins. These studies indicated that there was a group of high molecular weight proteins in the cytoplasm which bind to DNA with a degree of species specificity and also organ specificity. More recent studies suggest that there are fewer different DNA-binding proteins in the nucleoplasm than in the cytoplasm. A new approach to the problem has pursued the subfractionation of chromatin to elucidate how these DNA-binding proteins are affected by the aging process.

2. Dr. Tetsuo Hayashida, University of California, San Francisco, Calif.—This project studied the growth hormone levels in plasma, using the rat as the model system. The specificity of the radioimmune assay was improved, and the toxicity of the test system was reduced to negligible levels. These efforts will aid in the collection of more meaningful data about what happens to plasma growth hormone levels during the aging process.

3. Dr. Louise P. Romanoff, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.—This investigation has found a significant reduction in adrenal and testicular hormones associated with aging in man. The capacity of these glands to produce steroids appears to be impaired because of the absence of important chemical building blocks from which the steroids are made. Diminished secretion of steroids can contribute to the intensity of arthritic conditions, impairment of bodily repair and reduced sexual drive.

4. Dr. Robert R. Klevecz, City of Hope National Medical Center, Duarte, Calif.—This project studied the binding of poly-L-lysine to small quantities of different chromation preparations. The findings support the hypotheses that nonhistone proteins act as derepressors through complexing with a constant amount of histone protein, which results in a loosening of the DNA-histone interaction. In hormone studies, cultured cells showed an increased doubling time, altered morphology, and a change in differentiation state. Studies of serine dehydratase activity supported the idea that enzyme induction can occur only at certain times of the cell cycle.

5. Dr. Adrian M. Ostfeld, Yale University, New Haven, Conn.—This project studied the health and psychosocial impact of forced relocation on aged people. Higher blood pressures among relocatees as compared to nonrelocatees were present shortly after relocation but diminished in 3 months and were absent in 1 year. A major new implication is the evidence of substantial malnutrition among relocatees occurring because of financial problems and/or the anxiety or depression of moving. The high alkaline phosphatase levels of the relocatees suggests osteomalacia, an observation which could be related to bone loss and frequent fractures of this group. After relocation, previously good marriages are reinforced and previously shaky marriages deteriorate. The intake of alcohol and tranquilizer-depressant drugs increases.

6. Dr. Lester Packer, University of California, Berkeley, Calif.—Studies of aging at the cellular level were conducted using human cells in culture as a model system. Vitamin E was found to greatly extend the life span of populations of these cultured cells. A direct correlation between accumulation of autofluorescent material in cells with decreased ability of cells to divide with increasing passage level was also discovered. Changes in lysosomal enzyme and DNA synthesis related to cell morphology has been correlated with cellular aging.

7. Dr. Jay Roberts, Medical College of Pennsylvania, Philadelphia, Pa.—Changes in membrane structure and function in the aging process were studied using an animal model. The calcium sensitivity of certain protein complexes was decreased in older animals which affects the contractile and modular proteins. In studies of the neural cell membrane, the corticol cyclic AMP, adenosine monophosphate, levels decreased with age. Studies of changes of cardiac membranes found that heart rate and the ventricular pacemaker of animals decreased with age.

8. Dr. John G. Stoffolano, University of Massachusetts, Amherst, Mass.—This project studied the neural and behavioral changes with aging using an animal model. The protein and carbohydrate intake was significantly affected by age, starting out low in young animals, gradually increasing, and then gradually decreasing with age.

9. Dr. Henry F. Epstein, Stanford University, Stanford, Calif.—Techniques for the purification of muscle proteins, paramyosin, myosin, and actin, have been developed to study the genetic control of the major contractile proteins and subsequently to understand muscle development and aging. A unique difference

between normal and mutant tryptophane synthetase A protein was found which will allow further studies of analysis of contractile protein.

10. Dr. Diego Segre, University of Illinois, Urbana, Ill.—This project studied changes in the immune response using the mouse as a model system. These studies were initiated in young mice in which the numbers of antibody forming cells and the quality of the antibodies have been determined. Sites of age-related immunologic defects in terms of cell type and noncellular environmental factors are being identified.

11. Dr. Merrill F. Elias, Syracuse University, Syracuse, N.Y.—This investigation has an objective of utilizing a reaction time pattern to provide an experimental test of verbal and nonverbal processes in elderly persons. The relative degree of impairment of multiple cognitive functions within age groups was studied so that specific mental functions such as data storage and selective retention may be identified. A slowing of response with advancing age for tonal and visual assays was demonstrated. Age differences in time to match auditory stimuli were basically related to time required to search secondary memory for the rules for matching stimuli.

12. Dr. Elizabeth S. Russell, Jackson Laboratory, Bar Harbor, Maine—This study of the aging process utilized the mouse as a model system. Progressive changes in behavior occurring with age were observed and a genetic reason for this is being investigated. It has been suggested that age-dependent changes are the result of failure of the thyroid to respond to thyrotropin and a secondary failure of the pituitary to respond to decreasing levels of plasma-bound iodine. Other studies of the functional capacity of hematopoietic stem cells led to the conclusion that marrow precursor cell lines do not show intrinsically timed aging.

Mr. MICHEL. I guess we have to look at the results at the end of the road.

Dr. KRETCHMER. Certainly.

Mr. OBEY. How many approved grants could not be funded this year because of dollar limitations in the Aging Institute?

Dr. KRETCHMER. In the National Institute on Aging for 1975 we will have approximately 30 unfunded approved grants with a total value of $1,650,000.

Mr. OBEY. How many are in the high priority bracket?

Dr. KRETCHMER. These would all be approved but not funded, and therefore, in the high priority bracket.

Mr. OBEY. What are some of those?

Dr. KRETCHMER. Off hand Mr. Obey, I do not know what the titles of those grants are.

Mr. OBEY. I would like a few examples for the record.

Dr. KRETCHMER. Surely.

[The information follows:]

NATIONAL INSTITUTE ON AGING

EXAMPLES OF HIGH PRIORITY UNFUNDED RESEARCH GRANTS

Following are examples of high priority unfunded competing regular research grants in 1975:

1. A study to investigate the effects of large doses of Vitamin E on survival, life span, and fertility. As such this study would not be appropriately conducted in man, so the laboratory rat will be utilized.

2. A proposal to take advantage of a unique opportunity to examine the relationship between aging at the level of the cell and a genetic defect which results in a disease identified as Bloom's syndrome, an aberration of the chromosomes. It is hoped to answer the question of whether defects of this kind will affect cell aging as studied in cell culture systems.

3. A study, using the rat as a model system, to examine nuclear proteins and DNA from liver, thymus, brain and bone marrow of the aging animals. This

proposed study may clarify the existing controversial information concerning changes in a certain category of cellular molecules, the nuclear proteins, during aging.

4. A proposal to measure the production of certain very important molecules within the organism. It will measure rates of fatty acid and cholesterol synthesis in the rat as a function of age.

5. A proposal to pursue investigations of age-related changes in muscles. These studies will be conducted at the biochemical level, comparatively, on a number of different mammal model systems—rats, rabbits, cats, and dogs.

6. A study to test one of the basic theories of aging which suggests that the immune system of the organism to a greater or lesser degree acts against the organism's own cells and that such autoimmune activity, through time and with sufficient intensity, may be a major contributor to the aging process.

7. A proposal to investigate cell surface function as it relates to aging in human cells that are cultured outside of the body. The membranes that delimit individual cells within the body have proved to be very significant in all aspects of health and disease research. Cell membrane integrity and characteristics are integral to cell function and viability and are likely significant to the aging process. This project will study the ability of the membrane to transport nutrients from the cell culture environment into the cell itself for further processing.

8. A study to investigate the nutritional needs of the aging human; specifically, it will study requirements for protein, energy, protein-energy relationships, calcium, calcium-protein interrelationships, and certain trace minerals.

9. A study to pursue the important area of the significance of prenatal nutrition on aging and longevity. The study will include specific aspects of aging in the brain of first and second generation rats whose dams have been variously restricted in protein, calories, or essential amino acids during pregnancy. This proposal takes into consideration that aging is not merely confined to the latter portion of a lifespan, but rather is probably consequent to the state of health from conception onward. Investigation of this type will contribute to our understanding of this phenomenon.

10. A study to pursue research in the age-dependent changes in some of the most significant of the materials making up the body, the primary tissue proteins, namely collegen, elastin, and glycoprotein. Although it is generally appreciated that an individual is made up of a great number of numerous types of interacting cells, it is sometimes less appreciated that the body structure and form relies very much on molecules and mineral deposits which are external to the cells.

APPOINTMENT OF DIRECTOR

Mr. CONTE. Dr. Kretchmer, can you tell us when a director of the Institute will be appointed? What seems to be the delay?

Dr. KRETCHMER. Many potential candidates have been interviewed. Eight offers have been made to date. Dr. Lamont-Havers has indicated that the $36,000 salary ceiling is a major reason why individuals have rejected the offers. However, we are continuing the search.

PERSONNEL

Mr. CONTE. Do you feel that there is a sufficient number of competent staff members on board to carry out the responsibilities with which you have been charged?

Dr. KRETCHMER. We have a competent staff, over 90 percent of whom are bench scientists and supporting personnel at the Gerontology Research Center. With this distribution between intramural and extramural staff, then, we do not have the requisite number of people to carry out effectively the mandates of the Research on Aging Act, in particular to establish the NIA. We feel that an additional 30 to 35 positions are needed to meet this mandate.

RESEARCH GRANTS

Mr. CONTE. What percent of the approved grant applications do you expect to fund this year?

Dr. KRETCHMER. In 1975, the funding rate for approved competing research grants will be approximately 63 percent. We plan to fund approximately 17 percent of our approved competing research grants and only 75 percent of our noncompeting research grants in 1976.

MULTIYEAR FUNDING

Mr. CONTE. Are there any programs which require multiyear funding? What are those programs and amounts?

Dr. KRETCHMER. In 1975, we plan to multiyear fund one aging research project for approximately $150,000. For 1976, we do not anticipate any multiyear funding.

COORDINATION OF RESEARCH

Mr. CONTE. Would you tell me what other Institutes are carrying out research that affects the aged? How are you coordinating with these other Institutes? Is there any way to prevent overlaps and duplication?

Dr. KRETCHMER. Almost every Institute is carrying out research that affects the aged. These are defined within categorical disease areas, such as atherosclerosis which is a National Heart and Lung Institute endeavor. Our basic charge concerns study of the normal aging processes. However, there is close coordination among the Institutes to avoid unnecessary duplication.

DISSEMINATION OF INFORMATION

Mr. CONTE. How do you propose to disseminate the results of your research into the health care delivery system?

Dr. KRETCHMER. The dissemination of information will be of primary importance to the new Institute: only through sharing of information can research reach its logical clinical application. In 1976, we will continue to disseminate our research findings not only to the scientific and professional world, but to the public community as well. Although not related to the aging program, one example of what we have done in the National Institute of Child Health and Human Development is the extension of our education campaign on Down's syndrome (mongolism), which is aiming at several segments of the population, including physicians and mothers at high risk for producing offspring with Down's syndrome. In addition, the information campaign on the sudden infant death syndrome has continued to reach all segments of the community, medical, scientific and lay.

RESEARCH FOCUS

Mr. CONTE. To what extent is your research focused on the increase of life expectancy, as opposed to maintaining health and productivity through existing life spans?

Dr. KRETCHMER. Our goal is to have an elderly population that is healthy, productive, and happy. We are not attempting, as a goal, to increase the life span although some of our research results may eventually have a modest impact on life expectancy. I believe that the major impact on increasing life expectancy will come from research, in such areas as heart disease and cancer, which is covered by other research Institutes.

INTERAGENCY COMMITTEE ON AGING

Mr. CONTE. Would you tell me which agencies are participating in your Interagency Committee on the Aging?

Dr. KRETCHMER. Certainly. The participating organizations are: The National Institute on Aging, the Administration on Aging, the Office of Nursing Home Affairs, the Federal Council on Aging, the Assistant Secretary for Health's Office of Policy Development and Planning, the Office of the Assistant Secretary for Planning and Evaluation, the Medical Services Administration, the Office of Research and Statistics of the Social Security Administration, the National Institute of Mental Health, the Food and Drug Administration, the National Center for Health Services Research, and the Health Services Administration.

INTRAMURAL RESEARCH

Mr. CONTE. Would you provide a more detailed description of functions being studied at the Georontology Research Center?

Dr. KRETCHMER. Almost every organ system of the body is now being evaluated with respect to changes associated with age in normal human subjects. For example, detailed tests of heart function, lung function, kidney function, and muscle function are being conducted at specified intervals in a group of 650 males ranging in age from 20 to 96 years. Many of the tests are new ones that have been developed at the Gerontology Research Center in order to provide a more precise index of the function of the organ system under study. In addition to tests in specific organ systems, other tests are applied to study the integrated activity of a number of organ systems. For example, in addition to muscular strength, the ability to perform muscular work is measured. Psychological tests of mental performance are also administered. These tests include ability to learn new material, the ability to solve complicated problems, and tests of both long and short term memory. All subjects are tested for hearing and vision, including a test for glaucoma. Standard clincial laboratory tests of blood sugar, cholesterol, serum protein, blood creatinine, and nonprotein nitrogen are performed as well as chest X-rays, bone density measurements, and electrocardiograms, to provide information to identify early states of disease in the subjects. Detailed diet records are kept by the subjects which permit an analysis of food intake, the adequacy of the diet and its relationship to the development of obesity. At present, some 85 specific tests are administered to each subject. As new tests are developed they are introduced into the program so that new and more precise information about each subject is obtained.

Mr. CONTE. Do you foresee the development of more diagnostic tests?

Dr. KRETCHMER. Although the program of the Gerontology Research Center is focused on the effects of aging on relatively well people, it is highly probable that many of the new tests which are being developed will be of value in the early diagnosis of diseases such as diabetes, heart disease, arteriosclerosis, and hypertension. For example, a chart has been developed from tests made of subjects in the longitudinal study which is of great help to physicians in diagnosing diabetes, especially in older people.

Mr. CONTE. What kind of studies are you conducting on the role of the male sex hormone on the proneness to heart disease?

Dr. KRETCHMER. Since females live, on the average, 7 to 8 years longer than males, we are conducting experiments to see whether this difference is due to the effects of male or female sex hormone or is a result of other genetic differences between males and females. Before the age of menopause females show a much lower incidence of cardiovascular disease than do males. However, after menopause the incidence of heart disease in females increases so that by age 65 to 70 the rates for males and females are about the same. It is in this context that studies on physiological differences between males and females are planned for future expansion of program.

Mr. CONTE. How long do you plan to continue the longitudinal study at the Gerontology Research Center?

Dr. KRETCHMER. The value of a longitudinal study increases greatly the longer the subjects can be studied, because the characteristics of the individual can be more precisely determined with increasing observational points. Furthermore, there is an increased opportunity for observation of the effects of specific events, such as loss of spouse, retirement, changes in job, and other occurrences in daily life. Many diseases seen in the elderly may have a genesis earlier in life. It is only by following middle age into old age and senescence that the effects of these early events can be determined. In order to reap the full benetfis of a longitudinal study, especially in predicting the occurrence of diseases later in life, it must be looked upon as a continuum. It is my professional judgment that any serious study of aging in the human must include a continuing longitudinal program.

Mr. CONTE. Would you describe how you use the biofeedback technique to control hypertension?

Dr. KRETCHMER. The biofeedback technique consists of providing information to the subject about his blood pressure. Recording equipment is attached to his arm which shows on the dial his blood pressure at 1-minute intervals. The subject is simply instructed to make every effort to cause the needle on the dial to drop. After extensive training sessions some subjects have learned a technique which will produce lowering of his pressure at will. No specific instructions are given to the subject since each finds a different approach to the problem. It must be emphasized that this technique is still in the experimental stage, and further research must be conducted before it can be regarded as an effective treatment for general use.

DISEASES OF THE ELDERLY

Mr. CONTE. Would you tell me what diseases are particularly problematic for the aged?

Dr. KRETCHMER. The diseases most problematic for the aged are those most responsible for death among persons 65 years of age and older. These are heart disease; cancer; stroke; influenza and pneumonia; arteriosclerosis; diabetes; bronchitis, emphysema, and asthma; cirrhosis of the liver; and infections of the kidney. Although not identified as a disease, accidents take a severe toll among the aged, apparently because of age-related decrease in reaction time, losses of sight and hearing, and similar problems. Other problems would include arthritis; dental disease; vision, hearing, and sleep disorders; senile dementia; and depression.

Diseases of the aged are not the specific domain of the aging research program, as these have been singled out for particular attention and are pursued through other categorical institutes of the NIH. It is a part of the mission of the National Institute on Aging to pursue research leading to an understanding of the normal senescence process in people which predisposes them to these diseases.

HEALTH CARE FUNDING

Mr. CONTE. As you mentioned in your statement, about two-thirds of all Federal health care funds are directed toward persons over age 65. Do you think this is appropriate, or should more or less funding be directed this way?

Dr. KRETCHMER. Responsibilities of the National Institutes of Health lie in the fields of biomedical research. Because we recognize this question to be of great potential significance, we hope that through the research efforts of the new NIA significant advances are made to provide a healthier life for the aged, thus reducing the Federal costs for health care.

Mr. CONTE. What portion of our population is over age 65?

Dr. KRETCHMER. Approximately 10.5 percent of the population is 65 or older.

Mr. CONTE. What percentage of our health care needs would you estimate are among those 65 and older?

Dr. KRETCHMER. There are no comprehensive data to respond in detail to your question. However, 30 percent of the total health care dollar expenditure goes to this age group or 10.5 percent of the population. It should be recognized that medicare now pays 40 percent or less of this total health care bill, the reason being that it covers only a small portion of long-term care. Any revision in health care systems can be anticipated to result in a substantial increase in the percent of the total health care bill going to the aged, since such changes are expected to increase long-term care coverage. Long-term care coverage becomes generally more significant to older people because they have more chronic health problems.

NATIONAL ADVISORY COUNCIL ON AGING

Mr. CONTE. Would you describe the work of the National Advisory Council on Aging?

Dr. KRETCHMER. The purpose of the National Advisory Council on Aging is to advise, consult with, and make recommendations to the Secretary of HEW on programs relating to the aged which are administered by the Department. Its functions include, in addition, the review of grants and contracts, and the development of a comprehensive plan for a research program on aging.

RESEARCH PLAN

Mr. CONTE. What is the status of this comprehensive plan for aging research?

Dr. KRETCHMER. Several meetings have been held by the Interagency Committee on Aging and the National Advisory Council on Aging to lay the groundwork for the plan. At this time, it is in its formulation stage, and we hope to have completed the plan by the end of May.

Mr. CONTE. Do you consider it appropriate to continue with aging research before that comprehensive plan is completed? Can you be sure that present research would be considered important under that plan?

Dr. KRETCHMER. The current efforts represent the foundation of the new institute. Although priorities may be changed and new initiatives may be identified by the plan, drastic program alterations are not expected; and, given current budget and position constraints, it is only possible to maintain the status quo in 1976.

SENILE DIMENTIA

Mr. CONTE. Your justification states that available leads must be vigorously followed in investigating mental senility. What are those leads so far?

Dr. KRETCHMER. Several leads are considered significant and warrant continued research. There is a loss of synaptic contacts between brain cells, and also a loss of neurons, both in normal and senile aging. These factors suggest a relationship to loss of brain function and of mental capacity. A brain antibody appears in the blood serum which may haxe cytotoxic effects, perhaps explaining in part the decrease of neurons. Abnormalities of proteins develop in the tubules within nerve cells that become twisted and packed, known as neural-fibulary tangles, and also in soluble proteins of the brain. Extracellular amyloid plaques and high levels of aluminum appear in the senile brain. These changes of proteins as well as the accumulation of aluminum may directly affect brain function.

Mr. CONTE. How much will be spent this year on senility research? How does this compare to last year?

Dr. KRETCHMER. There will be little difference in expenditures on senility research in 1974, 1975, and 1976. We will spend approximately $200,000 in each of those years.

AGING AND THE IMMUNE SYSTEM

Mr. CONTE. Your justification refers to the effect of caloric restriction in delaying deterioration of the immune system in animals. Is there any evidence that this may also be true in humans?

Dr. KRETCHMER. There is no direct evidence that caloric restriction delays the deterioration of the immune system in humans, although there are some suggestions that this may occur. A well documented population of long-lived humans in a mountainous region of Ecuador is comprised of individuals who eat a primarily vegetarian, low-calorie diet of approximately 1,900 calories per adult each day, and perform heavy physical labor. This population is of interest to gerontologists; however, there is no evidence as yet to associate this correlation of low calorie diet and unusual longevity with a specific mechanism such as delaying the deterioration of the immune system.

Mr. CONTE. Could there be a relationship between overweight and the demise of the immune system?

Dr. KRETCHMER. Yes; there could be a relationship between the demise of the immune system and obesity. Research on animals has demonstrated that the immune system maintains its young characteristics longer in animals subjected to dietary restrictions, that is, not overfed. It is possible that a similar relationship would exist in the human.

POPULATION TRENDS

Mr. CONTE. Do you have any estimates regarding what portion of our population might be over 65 in the long run, say 20 or 30 years from now?

Dr. KRETCHMER. The projection for July 1975, is that there will be 22.3 million persons 65 years and over in the United States, which would be 10.5 percent of the total population. By 1990, there will be an estimated 28.9 million persons 65 years and over, 11.8 percent of the population.

OFFICE OF HUMAN DEVELOPMENT

Mr. CONTE. To what extent do you interact with the Office of Human Development? How do you coordinate efforts?

Dr. KRETCHMER. Interaction and coordination is accomplished through the Interagency Committee on Aging. The extent of interaction is sufficient to achieve effective administration of aging research programs.

Mr. CONTE. Do you have any programs underway in elderly nutrition?

Dr. KRETCHMER. Yes. In the longitudinal study at the Gerontology Research Center all subjects provide a record of all food eaten during a 1-week period. These records are analyzed to calculate the amount

of protein, carbohydrate, fat, minerals, and vitamins that have been consumed by each subject. Preliminary analysis of the data indicates that with increasing age the total caloric intake tends to fall. Although no gross vitamin deficiencies have been observed, the number of subjects with marginal intakes increases with age. It is also found that older subjects who take vitamin supplements have higher blood levels of these vitamins than do subjects who take no supplements. Ultimately we hope to relate dietary intake and habits to the overall physiological status in the elderly. In addition, we have a project specifically studying the protein needs of the elderly.

Mr. CONTE. Are the results of such studies being inputed to the human development elderly nutrition program?

Dr. KRETCHMER. Research results in the field of nutrition and the elderly which progress to a stage warranting either clinical trial or broad implementation will be communicated to the human development elderly nutrition program through the Interdepartmental Committee on Aging Research. Advances in knowledge of nutrition in the elderly, achieved through NIH supported aging research, will be communicated to the scientific community and nutrition professionals through scientific journals.

Mr. OBEY. Thank you.

Mr. FLOOD. Thank you, Dr. Kretchmer.

Dr. KRETCHMER. Thank you, Mr. Chairman.

Appropriation Estimate

NATIONAL INSTITUTE ON AGING

To carry out, except as otherwise provided, title IV, parts H and I of the Public Health Service Act with respect to aging, $16,190,000.

For the "National Institute on Aging" for the period July 1, 1976, through September 30, 1976, $4,048,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Amounts Available for Obligation[1/]

	1975 Estimate	1976 Estimate
Appropriation	---	$16,190,000
Comparative transfer from:		
"National Institute of Child Health and Human Development" (Transfer of aging activities in accordance with the Research on Aging Act of 1974)	$15,722,000	---
Total, obligations	15,722,000	16,190,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 comparable - $2,000; 1976 - $2,000.

Summary of Changes

1975 Estimated obligations	$ 15,722,000
1976 Estimated obligations	16,190,000
Net change	+468,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1975 pay, FICA, and health benefits increases	--	---	--	+$61,000
2. Within-grade pay increases	--	---	--	+102,000
3. Wage Board pay increases	--	---	--	+1,000
4. One extra day of pay and costs of new Council	--	---	--	+18,000
5. Bureau of Employee Compensation	--	---	--	+1,000
6. Increased cost of postage	--	---	--	+1,000
7. Federal Telecommunications System	--	---	--	+2,000
8. Gerontology Research Center maintenance contract	--	---	--	+111,000
Subtotal	--	---	--	+297,000
B. Program:				
1. Research grants:				
a. Noncompeting continuations	--	$3,875,000	--	+4,947,000
b. Competing (new, continuations, and supplementals)	--	3,717,000	--	+1,852,000
2. Fellowships:				
Noncompeting continuations	--	661,000	--	+6,000
Subtotal	--	---	--	+6,805,000
Total, increases	--	---	--	+7,102,000

Summary of Changes - Continued

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Decreases:				
A. Built-in:				
1. Payment to "National Institutes of Health Management Fund".....	--	---	--	-21,000
Subtotal.....	--	---	--	-21,000
B. Program:				
1. Research grants:				
a. Noncompeting completed, converted to competing status or terminated.....	--	3,875,000	--	-2,737,000
b. Competing completed or converted to noncompeting.	--	3,717,000	--	-3,717,000
2. Fellowships:				
Noncompeting completed.....	--	661,000	--	-38,000
3. Training Grants:				
Noncompeting completed.....	--	1,156,000	--	-23,000
4. Research Contracts.....	--	800,000	--	-98,000
5. Positions.....	175	---	-2	---
Subtotal.....	--	---	-2	-6,613,000
Total, decreases.....	--	---	-2	-6,634,000
Total, net change.....	--	---	-2	+468,000

Explanation of Changes

Increases:

A. Built-in: These increases will provide: $61,000 ($53,000 in Intramural, laboratory and clinical research and $8,000 in Research management and program services) for annualization of the 1975 pay, FICA, and health benefits increases; $102,000 ($90,000 in Intramural, laboratory and clinical research and $12,000 in Research management and program services) for within-grade pay increases in 1976; $1,000 in Intramural, laboratory and clinical research for wage board pay increases; $18,000 ($15,000 in Intramural, laboratory and clinical research and $3,000 in Research management and program services) for one extra day of pay in 1976 including an increase in cost for the new NIA Council;
$1,000 in Research management and program services for Bureau of Employee Compensation increases; $1,000 in Research management and program services for the increased costs in postage; $2,000 in Research management and program services for the increased costs in the Federal Telecommunications System; and $111,000 for increased rates in the Intramural, laboratory and clinical research's Gerontology Research Center's maintenance contract.

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Explanation of Changes - Continued

B. Program:

1. Research Grants:

a. The increase of $4,947,000 in noncompeting regular research grants represents the increased cost for continuation of previously awarded grants plus "new" continuation awards.

b. The amount of $1,852,000 in competing regular research grants in 1976 will permit the funding of high priority competing awards.

2. The increase of $6,000 for noncompeting fellowships represents the increased costs for continuation of previously awarded fellowships.

Decreases:

A. Built-in: The decrease of $21,000 (-$77,000 in Intramural, laboratory and clinical research and +$56,000 in Research management and program services) in payment to the NIH Management Fund reflects a decrease in the National Institute on Aging's proportionate share of the cost for centrally furnished services.

B. Program:

1. Research grants:

a. The decrease of $2,737,000 consists of $1,163,000 for noncompeting regular research grants that were completed in 1975 or that are being converted to competing status in 1976; and $1,574,000 for termination of research grants.

b. The decrease of $3,717,000 reflects the completion or conversion to a noncompeting status of competing grants awarded in 1975.

2. The decrease of $38,000 in noncompeting fellowships represents noncompeting awards which were completed in 1975.

3. The decrease of $23,000 in noncompeting training grants represents the phase-out of this program after the training under previously approved training grants is completed.

4. The decrease of $98,000 in research and development contracts reflects a reduction in the number of new contracts that will be awarded.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
116	Aging.....	--	$10,307,000	--	$10,499,000	--	+$192,000
121	Intramural, laboratory and clinical research.	160	4,548,000	158	4,741,000	-2	+ 193,000
126	Research management and program services.....	15	867,000	15	950,000	--	+ 83,000
Total obligations.....		175	15,722,000	173	16,190,000	-2	+ 468,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	175	173	-2
Full-time equivalent of all other positions	26	30	+4
Average number of all employees	197	199	+2
Personnel compensation:			
Permanent positions	$ 2,248,000	$ 2,386,000	+$138,000
Positions other than permanent	131,000	140,000	+ 9,000
Other personnel compensation	56,000	60,000	+ 4,000
Subtotal, personnel compensation	2,435,000	2,586,000	+ 151,000
Personnel benefits	314,000	346,000	+ 32,000
Travel and transportation of persons	80,000	62,000	- 18,000
Transportation of things	24,000	50,000	+ 26,000
Rent, communications, and utilities	50,000	60,000	+ 10,000
Printing and reproduction	40,000	40,000	---
Other services:			
Project contracts	800,000	702,000	- 98,000
Payment to NIH management fund	798,000	777,000	- 21,000
Other	914,000	1,020,000	+ 106,000
Supplies and materials	525,000	525,000	---
Equipment	235,000	225,000	- 10,000
Grants, subsidies, and contributions	9,507,000	9,797,000	+ 290,000
Total obligations by object	15,722,000	16,190,000	+ 468,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1975 House Report	
1. The Committee was concerned that the National Institute of Child Health and Human Development has not done enough aging research (pages 39 and 40).	1. In accordance with the Research on Aging Act of 1974, aging research activities of the National Institute of Child Health and Human Development will be transferred to the National Institute on Aging in 1976. In 1976, the Institute will spend approximately $16,190,000, an increase of $468,000 over the 1975 level of $15,722,000.
1975 Senate Report	
1. The Committee expressed concern that aging research was not receiving adequate attention (page 61).	1. In accordance with the Research on Aging Act of 1974, aging research activities of the National Institute of Child Health and Human Development will be transferred to the National Institute on Aging in 1976. In 1976, the Institute will spend approximately $16,190,000, an increase of $468,000 over the 1975 level of $15,722,000.

Authorizing Legislation

Legislation	1976 Authorization	1976 Appropriation Requested
Public Health Service Act Section 301 - Research and Investigation, in general	Indefinite	
Title IV, Part H - National Institute on Aging	Indefinite	$14,428,000 2/
Title IV, Part I - National Research Service Awards	1/	1,762,000 2/

1/ Authorization expires June 30, 1975; extension legislation is proposed.

2/ Funding estimate only.

National Institute on Aging

COMPARABLE

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1975 A/	$14,628,000	$14,922,000 B/	$16,552,000	$15,722,000
1976	16,190,000			

NOTES: A/ Because of the change in the budget structure from mechanism to program in 1975, comparable National Institute on Aging estimates are reflected beginning in 1975.

B/ Excludes research and development contracts which were not considered by the House due to lacking authorization.

National Institute on Aging

ACTUAL

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1976	$16,190,000			

Justification

National Institute on Aging

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	175	$ 2,749,000	173	$ 2,932,000	-2	+$183,000
Other expenses.....	--	12,973,000	--	13,258,000	--	+ 285,000
Total.....	175	15,722,000	173	16,190,000	-2	+ 468,000

General Statement

The Research on Aging Act of 1974 (P.L. 93-296) was signed into law on May 31, 1974. By passage of this Act, the Congress finds and declares that -

(1) The study of the aging process has not received research support commensurate with its effects on the lives of every individual;

(2) Various factors associated with aging operate to exclude millions of older Americans from the full life and the place in our society to which their years of service and experience entitle them;

(3) Recent research efforts point the way toward alleviation of the problems of old age by extending the healthy middle years of life;

(4) There is no American institution that has undertaken comprehensive systematic and intensive studies of the biomedical and behavioral aspects of aging and the related training of necessary personnel;

(5) The establishment of a National Institute on Aging within the National Institutes of Health will meet the need for such an institution.

The objectives of this Act are: (a) to establish the National Institute on Aging with full Institute status and responsibilities; (b) to establish a National Advisory Council on Aging; (c) to develop within one year a research plan designed to coordinate and promote research into the biological, medical, psychological, social, educational, and economic aspects of aging; (d) to conduct scientific studies to measure the impact on the biological, medical and psychological aspects of aging of all Departmental programs; (e) to assure the education and training of adequate numbers of allied health, nursing, and paramedical personnel in the field of aging; and (f) to carry out public information and education programs relevant to aging.

The National Institute on Aging was established on October 7, 1974. Aging research activities of the National Institute of Child Health and Human Development, including extramural grant and contract programs and intramural research conducted at the Gerontology Research Center, have been transferred to the National Institute on Aging and will become the focus of aging research in the

Federal government.

Within the next 50 years, the number of persons in the United States over 65 will increase to 40 million. Two-thirds of the Federal money spent on health care in this country is spent on persons over 65. One million persons over 65 live in institutions and a significant portion of these are incapacitated by senile dementias. The aim of the research program on aging is to enable these older persons to enjoy good health and remain participating members of society. The degenerative aging processes that begin early in life, and whose results surface as disabilities in middle and late life, must be studied and understood in such depth that they can be slowed or ameliorated.

DHEW - National Institutes of Health

CROSSWALK - 1975 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute on Aging
(in thousands)

Program \ Mechanism	Research Grants						Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials		Training Programs					
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Aging	$3,875	$3,717		$98	$1,156	$661		$800		$10,307
2. Intramural, laboratory and clinical research							$4,548			4,548
3. Research management and program services									$867	867
Total obligations	$3,875	3,717		98	1,156	661	4,548	800	867	15,722

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute on Aging
(in thousands)

Program \ Mechanism	Research Grants						Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials		Training Programs					
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Aging	$6,085	$1,852		$98	$1,133	$629		$702		$10,499
2. Intramural, laboratory and clinical research							$4,741			4,741
3. Research management and program services									$950	950
Total obligations	6,085	1,852		98	1,133	629	4,741	702	950	16,190

National Institute on Aging

Budget Mechanism

	1975 Number	1975 FTE[A/]	1975 Amount	1976 Number	1976 FTE[A/]	1976 Amount
Grants						
Regular						
Non-competing	41		$ 3,875,000	58		$ 6,085,000
Competing	14		1,280,000	6		596,000
New	35		2,387,000	16		1,206,000
Supplemental	(2)		50,000	(2)		50,000
Subtotal	90		7,592,000	80		7,937,000
Special						
Research career programs	3		75,000	3		75,000
Scientific evaluation	--		23,000	--		23,000
Subtotal	3		98,000	3		98,000
Total research grants	93		7,690,000	83		8,035,000
Fellowships						
Non-competing	29		409,000	45		629,000
Competing	--		---	--		---
New	18		252,000	--		---
Supplemental	--		---	--		---
Subtotal	47		661,000	45		629,000
Training grants						
Non-competing	18	78	1,156,000	18	76	1,133,000
Competing	--		---	--		---
New	--		---	--		---
Supplemental	--		---	--		---
Subtotal	18	78	1,156,000	18	76	1,133,000
Intramural, laboratory and clinical research	--		4,548,000	--		4,741,000
Research and development contracts	--		800,000	--		702,000
Research management and program services	--		867,000	--		950,000
Total	--		15,722,000	--		16,190,000

A/ Full-time equivalents

Aging

Authorizing Legislation: Public Health Service Act, Title IV, Parts H and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits	--	---	--	---	--	---
Other expenses	--	$10,307,000	--	$10,499,000	--	+$ 192,000
Total	--	$10,307,000	--	$10,499,000	--	+$ 192,000

Budget Mechanism:

Research Grants:						
Regular:						
Noncompeting	41	3,875,000	58	6,085,000	+17	+ 2,210,000
Competing	49	3,717,000	22	1,852,000	-27	- 1,865,000
Special	3	98,000	3	98,000	--	---
Subtotal	93	7,690,000	83	8,035,000	-10	+ 345,000
Fellowships	47 A/	661,000	45 A/	629,000	- 2 A/	- 32,000
Training Grants	78 A/	1,156,000	76 A/	1,133,000	- 2 A/	- 23,000
Research & Development Contracts	12	800,000	11	702,000	- 1	- 98,000
Total	--	10,307,000	--	10,499,000	--	+ 192,000

A/ Full-time equivalents

Introduction

Biologic aging affects all humans, progressively degrading their functional competence, and the decrements produced have profound medical, psychological, and social consequences. Biologic aging literally shapes the lives of individuals and the overall function of society.

In the early decades of adult life, the decrements are most obvious in physical performance where speed, strength, and endurance are especially important. However, functional decline pervades all human systems and can be measured by sensitive methods.

Despite physical losses humans become progressively more valuable to society for many years because of the time required to accumulate the knowledge and experience needed to function most effectively in society. Eventually, of course, when biologic deterioration overrides the value of a lifetime of learning, the elderly require special help from younger members of society.

The extramural program of the NIA supports research and research training aimed at 1) reducing the impact of biologic aging on health and functional capacity, 2) meeting the special health problems of the elderly and 3) facing the opportunities and problems that society will have if the fraction of older persons in the population increases.

The aging research program is accomplished through the award of research grants, fellowships, training grants, and research contracts, and the conduct of intramural research. The funds and description of programs for the intramural research effort are contained within the activity Intramural, Laboratory and Clinical Research. The funds to support the staff necessary to provide the scientific and administrative management of the aging program are contained within the activity Research Management and Program Services.

Program Plans, 1976

Research on aging in 1975 was supported largely through the extramural program of the National Institute of Child Health and Human Development. In 1976 it will be supported by the National Institute on Aging. Part of the Research on Aging Act of 1974 that led to the establishment of the National Institute on Aging requires the Secretary working with the National Advisory Council on Aging to prepare a comprehensive plan for aging research.

The initial extramural research program of the new Institute will consist of grants and contracts transferred from NICHD. Thus the initiatives and momentum established in that Institute can be maintained. However, the comprehensive plan prepared by the Secretary and Council plus continuing advice from the Council will play a major role in the Institute's direction.

In 1976 further studies of the molecular and cellular basis of aging will be made. There is a limit to the number of times the rapidly dividing cells of the mammalian body can reproduce by dividing. More scientists have progressively engaged in the task of determining the mechanisms involved in this limitation, and facts and theories concerning this phenomenon are being developed rapidly. An understanding of these mechanisms might throw light on the changes that occur in aging not only in rapidly dividing cells but also in non-dividing cells. If so, scientists would have a much firmer base for understanding the entire process of human aging.

Probably the most dreaded of the disabilities of old age is the mental senility which makes some elderly persons completely dependent for their maintenance on relatives or society. There are probably a number of different factors responsible for the senile dementias and they are difficult to disentangle both clinically and pathologically. The prevailing opinion now is that disease of the large arteries is not a common cause of senile dementia. Small artery disease and changes in the nerve cells themselves have been implicated, and it seems probable that other causes are involved. Whether a given case of dementia is due to a disease process or aging itself is usually obscure. In addition, psychologic depression may be confused for dementia. Across the entire span of adult years there appears to be a gradual decline in mental abilities. Whether some of the senile dementias are a continuation of this process or whether they represent something entirely different is not known.

Although the problems involved in studying mental senility are difficult, the results of i' are so serious that the available leads must be vigorously followed. A modest program on this condition already exists and will receive increased attention. Research success in this area might not only make it possible to prevent or treat mental senility but might also increase understanding of the aging processes that occur in the other non-dividing cells of the human body.

Research on the cells that provide the immunological defenses of the body, already receiving emphasis, will be continued and enriched to include the blood cell system. These latter cells are interesting in that some types develop from more primitive cells in the bone marrow and are released into the circulating blood when they have reached a high degree of specialization. As a result of the

specialization they have become non-dividing cells that are unusual in that they have short lifespans. Studies of these specialized cells would give insight into mechanisms of senescence of non-dividing cells. Studies of their precursors in the bone marrow would give information on the potential lifespans of these precursor cells and thus contribute further to knowledge of the factors involved in limited or unlimited division potential within human and other mammalian cells. The most immediate practical result of an increased understanding of immune and blood cells might be an increased ability to control infectious disease and cancer in older persons.

Studies on changes in endocrine competence will continue. The best known hormonal inadequacies of old age relate to the sexual hormones and to the control of carbohydrate metabolism by pancreatic synthesis and secretion of insulin. No doubt, the systematic investigation of the endocrine systems of the body will uncover other defects. An attractive feature of endocrine defects is that they can be treated by the administration of hormones which can be made available.

Program Plans, 1975

In research on causes and mechanisms of aging, efforts are concentrated on molecular and cellular processes. Even studies of organ systems such as the brain are now focused at molecular and cellular levels.

There is much evidence that the fundamental aspects of aging are similar in all mammals. Thus experimental studies on nonhuman mammals provide valuable insights into human aging. Rodents such as rats and mice are particularly useful for aging research because their short lifespans permit studies of aging to be completed rapidly.

The mammalian body contains three basic types of cells: rapidly dividing cells; slowly dividing cells; and cells that do not divide after the first few years of life. Biologists believe nondividing cells such as nerve and muscle cells are mortal with a potential lifespan probably not much longer than the lifespan of the animal of which they are part. Until recently they thought that rapidly dividing cells, such as the cells of bone marrow which produce red and white blood cells, would be immortal if it were not for the deterioration with age of the animal of which they are part. In other words, biologists thought that some cells making up the whole animal were mortal and others were potentially immortal. There are, indeed, mammalian cells that can be maintained indefinitely by transfer from young animal to young animal and thus appear to be immortal. However, all mammalian cells that have been shown to possess this attribute are either precancerous or cancer cells. So far, no normal mammalian cell types have been shown to possess potential immortality and a number of normal mammalian cell types have been shown to possess a finite ability to reproduce themselves and survive when repeatedly transplanted from young animal to young animal. It thus appears probable that all the normal cells may be mortal and the rejuvenation process that starts a new series of young cells may occur only in the course of the events that lead to a fertilized egg and eventually a new human. This does not mean that, if the processes involved in the senescence of cells were understood, they might not be influenced favorably. Research in this field may make it possible to reduce the impact of aging on human health. In 1975 progress is being made in understanding cellular aging in both dividing and nondividing mammalian cells. Studies of aging rat brains showed that with increasing age there was a great decrease in the number of the small anatomical processes which connect the nerve cells of the brain to each other. This discovery provides a lead that should be pursued in efforts to understand the basis of the loss of mental ability that occurs in the very elderly. Many studies are being carried out on the changes that occur in rapidly dividing cells with age. A number of structural, chemical, and functional changes have now been identified in such cells.

Eventually, it will be possible to say just what the process is that leads, even under the most favorable conditions, to the ultimate death of rapidly dividing mammalian cells. Control of this process may favorably influence human health.

Certain organ systems that show deterioration with age are receiving special attention in 1975. The immune system reaches its peak competence about the time of puberty or even earlier and thereafter gradually deteriorates until in old age it possesses only about a tenth of its peak efficacy. The immune system is important in protecting the human body against invasion by infectious agents and against those of the body's own cells that may become cancerous. One factor in the increased susceptibility of humans to infection and cancer with increasing age is a deteriorated immune system. It is possible even now to augment the human immune system by methods that are not specific to the defects occuring with aging. With an increased understanding of these defects more specific treatment may become possible. Recently, it was found that caloric restriction delayed the deterioration of the immune system that occurs with aging in experimental animals. This shows that it is possible to delay this aspect of aging. It suggests one way of doing so and offers the hope that other methods may be discovered.

An understanding of decreases in endocrine function with increasing age is especially useful because hormonal deficiencies can be compensated for by hormonal replacement therapy. An important endocrine change with age is ovarian atrophy which in the middle years of life leads to the development of the menopause. In 1975 the Institute is supporting studies of the treatment of the clinical manifestation of the menopause by the oral administration of female sex hormones.

The pattern of disease processes in the middle years of life is different from the pattern in later years. However, there is overlap so that there are few of any diseases that cannot occur in either period. The diseases of middle and old age are for the most part chronic diseases that are preceded by precursor conditions or activities which can be detected and in many cases modified. Control of these precursors, sometimes called risk factors, offers one of the major hopes of preventing or delaying the onset of chronic diseases. During 1975 the support of longitudinal studies to provide information on risk factors is continuing. One study reported that heavier weight-for-height, higher blood pressure, lower vital capacity, and parental history of diabetes are precursors of adult-onset diabetes mellitus, and that cigarette smoking, higher blood pressure, physical inactivity, and heavier weight-for-height were predictors of coronary disease.

Studies on changes in mental abilities are being undertaken. Of particular interest are studies suggesting that a significant factor in the poor performance on mental tests of some older people was an educational background inferior to that which was usual for the younger population with which they were compared. However, it is clear that intellectual deficits do occur at some point in the aging person and investigations of the characteristics and possible modification of those changes are being conducted in 1975.

In this country ten percent of the population is older than sixty-five years. In some European countries that figure has already reached sixteen percent. Reduced birth or death rates can both lead to a higher percentage although birth rate changes seem liable to produce the more striking changes in the age population of this country. Systematic studies to project future population age-structure and its probable impact on the individual elderly and society are underway.

The elderly, just as everyone else, may exhibit favorable or unfavorable responses to changes in their psychological, social, or physical environment. Although this is obvious, the changes are frequently more pronounced than anticipated or in an unexpected direction. An example of this was disclosed by studies of elderly persons who were to undergo involuntary relocation to better housing. Rather striking unfavorable changes in physiological characteristics such as blood pressure were found to be associated with anticipated geographical relocation.

Intramural, Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act, Title IV, Parts H and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	160	$2,507,000	158	$2,666,000	-2	+$159,000
Other expenses.....	--	2,041,000	--	2,075,000	--	+ 34,000
Total.....	160	4,548,000	158	4,741,000	-2	+ 193,000

Introduction

The Gerontology Research Center (GRC) located in Baltimore, Maryland comprises the Institute's intramural research effort.

Four laboratories and branches conduct the intramural research operations within the GRC. These include the Clinical Physiology Branch, the Laboratory of Molecular Aging, the Laboratory of Behavioral Sciences, and the Laboratory of Cellular and Comparative Physiology.

In addition to the laboratories and branches, the Guest Scientist Program at GRC, under which outstanding non-Federal investigators are invited to use the facilities of GRC to carry out research relevant to aging, has become an important part of this nation's aging research effort. During 1975, 18 Guest Scientist Programs were provided resources at GRC. Their activities, which are staffed by 27 senior investigators with 21 supporting personnel, included studies on age difference in cardiac performance, cell biology, gastrointestinal physiology, and endocrinology.

Program Plans, 1976

Clinical physiology - The clinical physiology endeavor is twofold: (1) gaining an understanding of the process of aging in man by finding answers to the following questions: (a) what are the changes in the functioning of multiple organ systems during the adult span of life? (b) why do these changes occur, that is, what are the underlying mechanisms responsible for these processes? (c) can these age changes be clearly differentiated from the onset of distinct disease processes of the later years? and (d) how does aging lead to disease development and to increased likelihood of death?; and (2) translating this understanding into effective techniques for amelioration or prevention of the deteriorative changes which accompany aging.

Planned continuation of current studies in the clinical physiology program will result in the following during 1976: (a) analysis of data collected from repeated measurements made over the past 12 years on subjects from the longitudinal program with special emphasis on serum cholesterol and triglycerides, glucose (sugar) tolerance tests, measures of adiposity and cellular mass, basal metabolism, lung function, and nutritional factors; (b) analysis of the interrelationships between the measurements made on the same subjects when analyzed longitudinally; (c) continuation of testing under the longitudinal study; (d) clarification of

relationships among four separate diagnostic tests for diabetes; (e) extension to human subjects of studies on cellular receptors for hormones; (f) development of a new method for the treatment of high blood pressure (a renin inhibitor); (g) studies on the role of the male sex hormone in proneness to heart disease and prostate hypertrophy; (h) studies on the use of echocardiography in assessing heart function in normal men of different ages; (i) studies of the mechanisms involved in the slowing of the rate of contraction of heart muscles observed in old rats; (j) determination of the role of calcium in regulating contraction of the heart muscle; and (k) studies of the response of the heart to hormones and drugs.

Molecular aging- The molecular aging activity investigates the molecular events that determine the rate of aging, and determine how these events affect individual organisms eventually leading to a decline or cessation of function.

In 1976, studies of the physiological and genetic transfer systems, based on techniques developed and findings made in 1975, will continue. Research will be directed to determine aging effects from changes in molecules which are essential for maintenance of cellular functions. New investigations will be designed to determine the effects of age on biochemical control mechanisms at the subcellular and cellular level. Studies of structural characteristics and the effects of age on structure of biological substances such as proteins, elastin, and connective tissue will be made.

Behavioral sciences- The behavioral sciences effort is directed toward an understanding of the factors which determine the decline in mental competence and self-sufficiency and to the development of methods for ameliorating these effects. Mental competence and self-sufficiency are two of the most prized possessions of man yet, along with physical health, are the most threatened by advancing age. In addition, several programs are designed to yield methods for dealing with a number of significant medical problems of the middle aged and elderly through the use of behavioral methods.

During 1976, the laboratory plans to determine the specific mechanisms which hypertensive patients utilize to lower their blood pressure. In addition, a study will be carried out to learn whether patients with irritable bowel syndrome can learn to relax their colonic muscles through biofeedback techniques, thereby obtaining clinically significant benefits from such training.

Projected studies will explore reasoning behavior where memory is also a factor. Other studies of learning and memory will attempt to relate these behaviors to physiological factors, such as high blood pressure, to determine whether these factors are correlated with behavioral changes.

Cellular and comparative physiology- This laboratory's program is threefold: (1) to conduct studies on the nature of the age-related deterioration of cells of the immune and related systems; (2) to determine the underlying cellular and molecular mechanisms responsible for this deterioration; and (3) to develop methods for early detection of signs of cellular aging and, hopefully, methods to control or reverse the harmful changes with aging leading to eventual cell malfunction or death.

Much of the work reported for 1975 will continue in 1976. In order to move forward in these areas, methodology and techniques will be developed and refined for a better understanding of the reasons why certain immunological and genetic changes take place.

Immunoengineering studies to correct the immuno-deficiency state of aging animals will focus on the mechanism of enhancing chemicals and on the rate of decline in immune functions following therapy.

Studies of the effects of age on enzymes will extend to various species including humans and various tissues including heart muscles. Studies will also take place that may lead to a better understanding of the role viruses play in the aging of individuals.

The immune system, which is intimately involved with adaptation of the body to environmental stress and change, declines in its efficiency with increasing age. Associated with this decline is the rise in susceptability to diseases such as infection caused by viruses and fungi, cancer, and self-destructive "autoimmune" diseases. Therefore, by accomplishing its goals this laboratory may be able to delay, reverse, or prevent the decline in normal immune functions. This in turn may delay the onset or lessen the severity of diseases accompanying old age.

Program Plans, 1975

Clinical physiology- The year 1975 will see the completion of the eighth 2-year cycle of testing in the Longitudinal Study of Human Aging. These studies are the most comprehensive analysis of the physiology of human aging ever undertaken. The diversity of studies is made possible by a remarkable group of 650 volunteers ranging in age from 20 to 90 years, who return to the Center for testing every 1 to 2 years depending upon their age. Results to date have provided the most reliable data on the definition of "normal aging" for many functions which are not only of importance to theories of aging but also to proper diagnosis and care of middle-aged and older patients.

Recently, for example, studies have been completed of the effect of age on the metabolism or disposition of drugs (medications) by the body. Possible age differences in the metabolism of alcohol and in the effects of alcohol on intellectual function and on physical performance had been almost totally neglected. It has been found that, unlike other chemicals, the disposition of alcohol does not change with age, but its effects on measures of attention, memory, and decision time are more severe in the aged. The concepts of a single blood level of alcohol which defines the intoxicated state may need to be adjusted to allow for these age differences in alcohol effect.

These alcohol studies have also demonstrated a defect with age in the physiology of the neurohypophyseal hormone, AVP, or the antidiuretic hormone. Alcohol was shown to decrease the production of this water-regulating hormone in young subjects but the effect could not be maintained in older subjects. Understanding of this disturbance in posterior pituitary gland function with aging will help in the treatment of serious distrubances of fluid balance which occur commonly in the older subjects.

Another drug study, just completed, illustrates the influence of the aging process. The drug, antipyrine, was found to disappear from the blood stream more slowly as age advanced. This age difference could be shown however to be largely due to differences in some of the "habits" of the young and old groups. Younger men tended to smoke more and drink more coffee, tea, and alcohol, than older men. These habits, especially cigarette smoking, were shown to influence the metabolism of antipyrine significantly. Without detailed histories of these habits, investigators would have erroneously concluded that the primary processes of biological aging had led to changes in drug metabolism; in fact, the changes were largely secondary effects. "Habits" will now have to be taken into account in the evaluation of the clinical pharmacology of drugs.

A new computer analysis of detailed dietary diaries kept by the participants in the longitudinal study showed that in subjects who did not take supplementary vitamins, seventy-two percent had a vitamin B_6 (pyridoxine) intake in their food

that was below the recommended level. Furthermore, the average intake in the oldest subjects was lower than that of the young adults. These data supplement and support studies in the same participants of the actual circulating blood levels of this vitamin. Further analyses will be forthcoming to test whether levels of the vitamin intake are too low or whether the recommended levels are set too high.

Data from participants in the longitudinal study show that kidney function as measured by creatinine clearance diminished progressively with age. These observations on normal subjects show clearly that the decrement is not a reflection of the increasing prevalence of kidney disease with age but is an effect of biological aging.

From these data, a chart has been developed which allows the physician to compute easily a score for each patient as compared with normal subjects of the same age. Use of this chart will help improve the diagnosis and treatment of kidney disease in older patients.

Studies on isolated heart muscle from the rat have shown that the tension developed with each beat is unaffected by age, but the time required to generate this tension is significantly prolonged in the aged heart. The mechanism of this prolonged contraction appears to be related to abnormalities in the active relaxing system, namely a delay in the removal of calcium from the contracting elements. Furthermore, the response to stress, elicited by exposure of the heart muscle to adrenalin, is significantly diminished in the aged heart.

Molecular aging- Aging results in part from the inability of an organism to maintain normal stable conditions in its internal environment. The laboratory is studying two critical biological functions known to suffer disturbances that affect the ability of organisms to maintain this stability. These systems are the physiological control system and the genetic information transfer system.

In studying physiological systems, this laboratory in 1975 developed techniques using animal models which may lead to an understanding of why the kidney of the elderly person fails to adapt and adjust as well as that of a younger person. The laboratory also studied the possibility that a change in the flow of calcium between cells may be a partial cause for the deterioration of cardiac function with age. A special device was developed by the laboratory to measure this flow.

In investigating genetic information transfer systems, the Laboratory of Molecular Aging studied how biological errors are caused in aged cells and found that synthetic polymers can be used to inhibit various steps in genetic information transfer, that takes place when cells divide. It is probable that the transfer of damaging characteristics from one cell to another can be inhibited through the use of these synthetic polymers.

Behavioral sciences- This laboratory holds a pre-eminent position in the world in the study of the clinical application of biofeedback (minor electric shock) techniques in the control of cardiac disorders. Clinical studies conducted in this program have shown that patients with high blood pressure can be trained to lower their blood pressure through biofeedback techniques without the use of drugs. In addition, it was shown that patients with severe fecal incontinence secondary to organic lesions can be taught to control, again through biofeedback techniques, their anal sphincters and therefore become continent. These findings can lead to significant relief for patients with this particular problem as incontinence is not only debilitating in a medical sense but also can have serious effects on a patient's personal, social and professional life. In fact this incontinence is often the deciding factor in commitment to a nursing home.

Multiple studies of reasoning behavior in man have shown that reasoning behavior, when looked at separately from memory changes, changes only in very old subjects. Studies have shown also that procedures can be identified which facilitate learning and memory for the old.

Cellular and comparative physiology- The thymus, which generates T lymphocytes, goes through a degenerative change throughout life after sexual maturity in humans and other animals. This is followed by a gradual decline in certain immune functions. Studies in progress have revealed that the degenerative changes are reversible for the most part. Based on this there may be a reasonable approach in delaying this decline in these immune functions.

An important, yet little understood problem in aging, is how scavenger cells recognize and destroy their own aging cells from the body. Evidence from studies in progress indicates that this recognition process is immunological in nature.

A systematic series of studies have been initiated to correct the immuno-deficiency state of old animals. Preliminary results indicate that certain immune functions can be rejuvenated by two different approaches: (1) the injection of a pharmacological agent; and (2) transplantation of young thymuses and injection of young stem cells from bone marrow.

The mouse has proven to be a good model for studying maternal age effect; i.e., the mechanism responsible for the increase in chromosomal alteration in children of older mothers. Preliminary results show that the frequency of mouse fetuses with chromosomal alteration rises over fourfold with increasing maternal age.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Title IV, Parts H and I

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	15	$242,000	15	$266,000	--	+$24,000
Other expenses.....	--	625,000	--	684,000	--	+ 59,000
Total.....	15	867,000	15	950,000	--	+ 83,000

This activity provides for the overall administration, direction, and coordination of the Institute's programs. It encompasses 1) the Director and his immediate staff concerned with administrative management, program planning and evaluation, and research information; and 2) the scientific and administrative staff responsible for grant and contract programming, review and administration.

Program Direction - This activity provides assistance and counsel to the Director in the fields of management, financial planning, program and statistical evaluation and analysis in the furtherance of the Institute's program. During 1976, this activity will continue to provide the necessary leadership and technical guidance.

Extramural - This activity provides the necessary professional and technical guidance for the processing, management, and scientific monitoring of the Institute's grant and contract programs. During 1975, approximately 158 grants, totalling $9,507,000 will be awarded. In addition, approximately $800,000 in research contracts will be awarded.

In 1976, this activity will continue to provide the required technical guidance in the furtherance of the Institute's grant and contract programs. During this period, approximately 146 grants will be awarded, totalling $9,797,000. In addition, $702,000 in research contracts will be awarded.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Program Purpose and Accomplishments

Activity: Aging (Public Health Service Act, Title IV, Parts H and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$10,307,000	Indefinite	---	$10,499,000

Purpose: The extramural program of the Institute is responsible for medical, biological, psychological, and social aspects of research relevant to the health of the elderly.

Explanation: The program supports research on the multitude of biological changes that occur with aging and are major determinants of disease processes, studies of cognitive and emotional alterations that occur with increasing age, and investigations of societal aspects of aging.

Accomplishments in 1975: Progress was made in understanding cellular aging. It now appears probable that all the normal cells that make up the human body may be mortal and that the rejuvenation process that starts a new series of young cells may occur only in the course of events that lead to a fertilized egg and eventually a new human. It was found that caloric restriction delayed the deterioration of the immune system that occurs with aging in experimental animals; this shows that it is possible to delay the immunological aspect of aging. Longitudinal studies reported results which showed that various factors such as high blood pressure and physical inactivity were predictors of coronary disease, and similar factors including high blood pressure and parental history of diabetes are precursors of adult-onset diabetes mellitus. Social and behavioral research results were also obtained. In a study of elderly persons it was found that unfavorable physiological changes were associated with anticipated geographical relocation.

Objectives for 1976: Studies of the molecular and cellular basis of aging will continue. An expanded effort regarding mental senility will be made. Immunological studies will be enriched to include the blood cell system. Also, studies on changes in endocrine competence will continue. Program direction will follow the comprehensive plan for aging research which is being formulated as a result of the Research on Aging Act of 1974.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Program Purpose and Accomplishments

Activity: Intramural, Laboratory and Clinical Research (Public Health Service Act, Title IV, Parts H and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
160	$4,548,000	Indefinite	158	$4,741,000

Purpose: The Intramural, Laboratory and Clinical Research activity comprises the Institute's intramural effort in aging research.

Explanation: The aging program, conducted at the Gerontology Research Center in Baltimore, includes research in cellular biology, biochemistry, physiology, and psychological development.

Accomplishments in 1975: Results of the longitudinal study have provided the most reliable data on the definition of "normal aging." Studies have shown the effect of age on the metabolism or disposition of various substances such as medications and alcohol by the body. Techniques have been developed in experimental animals which may lead to an understanding of why the kidney of the elderly person fails to adapt and adjust as well as that of a younger person. Progress has been made in training individuals with specific disorders such as high blood pressure and severe fecal incontinence to control the disorders themselves - without the use of medication. Studies have revealed that certain immune function degenerative changes are reversible for the most part.

Objectives for 1976: Clinical physiology activities will encompass many research avenues including: continuation of the longitudinal study; clarification of relationships among four separate diagnostic tests for diabetes; developing a new method for the treatment of high blood pressure; and the response of the heart to drugs and hormones. Investigations will continue to determine the molecular events that determine the rate of aging. Behavioral and social science endeavors will include investigations regarding: mental competence and self-sufficiency; hypertension; and learning and memory. Immunological studies will focus on: the nature of age-related deterioration of cells of the immune and related systems; the underlying cellular and subcellular mechanisms responsible for this deterioration; and the development of methods for early detection of signs of cellular aging.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Program Purpose and Accomplishments

Activity: Research Management and Program Services (Public Health Service Act, Title IV, Parts H and I)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
15	$867,000	Indefinite	15	$950,000

Purpose: This activity supports: 1) the Director and his immediate staff concerned with administrative management, program planning and evaluation, and research information; and 2) the scientific and administrative staff responsible for grant and contract programming, review and management.

Explanation: This activity provides the funds for salaries and other related operating costs for the overall administration and direction of the programs of the Institute.

Accomplishments in 1975: The staff supported by this activity continues to provide administrative management, program guidance and supportive services to the Institute's staff, in the furtherance of the Institute's goals. In 1975 it is estimated that 158 grants and 12 research contracts will be awarded.

Objectives for 1976: This activity will continue to provide for the coordination, administration, and direction of the Institute's research programs. In 1976, it is estimated that 146 grants and 11 research contracts will be funded.

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Amounts Available for Obligation[1/]

	1976 Estimate	Interim Period
Appropriation	$16,190,000	$4,048,000
Total obligations	16,190,000	4,048,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $2,000; Interim - $ 1,000.

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Aging	---	$10,499,000	---	$2,538,000
Intramural, laboratory and clinical research	158	4,741,000	158	1,255,000
Research management and program services	15	950,000	15	255,000
Total obligations	173	16,190,000	173	4,048,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	173	173
Full-time equivalent of all other positions	30	30
Average number of all employees	199	199
Personnel compensation:		
Permanent positions	$ 2,386,000	$ 600,000
Positions other than permanent	140,000	35,000
Other personnel compensation	60,000	15,000
Subtotal, personnel compensation	2,586,000	650,000
Personnel benefits	346,000	165,000
Travel and transportation of persons	62,000	20,000
Transportation of things	50,000	10,000
Rent, communications, and utilities	60,000	15,000
Printing and reproduction	40,000	10,000
Other services:		
Project contracts	702,000	100,000
Payment to NIH management fund	777,000	195,000
Other	1,020,000	320,000
Supplies and materials	525,000	100,000
Equipment	225,000	25,000
Grants, subsidies and contributions	9,797,000	2,438,000
Total obligations by object	16,190,000	4,048,000

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the National Institute on Aging consistent with the 1976 Estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY1975 modified by program impact of the FY1976 estimate.

FRIDAY, *April 18, 1975.*

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCE

WITNESSES

DR. DAVID P. RALL, DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
GEORGE M. KINGMAN, EXECUTIVE OFFICER, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
MRS. PEGGY J. McKINNEY, BUDGET ANALYST, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We will continue with the National Institutes of Health.

Next we have the National Institute of Environmental Health Sciences.

The presentation will be made by Dr. David P. Rall, the Director. We have a biographical sketch of you, Doctor, which we will place in the record at this point.

Name: David P. Rall, M.D., Ph. D.

Position: Director, National Institute of Environmental Health Sciences.

Birthplace and date: Aurora, Ill., August 3, 1926.

Education: B.A., North Central College, 1946; M.S., Northwestern University, 1948; Ph. D., Northwestern University, 1951; M.D., Northwestern University, 1951.

Experience: Director, National Institute of Environmental Health Sciences, 1971–present; Associate Scientific Director for Experimental Therapeutics, National Cancer Institute, 1966–71; Chief, Laboratory of Chemical Pharmacology, National Cancer Institute, 1963–69; Head, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute, 1958–63; Scientist, Clinical Pharmacology and Experimental Therapeutics Service, General Medicine Branch, National Cancer Institute, 1955–58; Scientist, Laboratory of Chemical Pharmacology, National Cancer Institute, 1953–55; research associate in pharmacology, Northwestern University, 1950; assistant in pharmacology, Northwestern University, 1949–50; Baxter fellow in pharmacology, Northwestern University, 1947–49.

Association memberships: Fellow, American Association for Advancement of Science; Society for Experimental Biology and Medicine; American Society for Pharmacology and Experimental Therapeutics; American Association for Cancer Research; American Society for Clinical Investigation; Federation of American Societies for Experimental Biology; Society of Toxicology; American Occupational Health Society; American Society for Clinical Pharmacology and Therapeutics; Washington Academy of Sciences.

Special awards, citations, or publications: Associate editor, Journal of Toxicology and Environmenal Health, 1974–present; Editorial Board, Archives

of Environmental Health, 1973–present; Chairman, DHEW Committee to Coordinate Toxicology and Related Programs, 1973–present; U.S. Coordinator, environmental health program U.S.–U.S.S.R. health exchange agreement, 1972–present; U.S. Coordinator, biological and genetic consequences project, U.S.–U.S.S.R. environmental protection agreement, 1972–present; U.S. Coordinator, U.S.–U.K. cooperative program in environmental health sciences, 1972–present; adjunct professor, University of North Carolina, Chapel Hill, 1972–present; Chairman, OST–CEQ, Ad Hoc Committee on Environmental Health Research, 1971–72; associate editor, Cancer Review, 1970–74; Chairman, HEW Departmental Committee on Drug Research and Regulations, 1970; editorial board, Pharmacological Reviews, 1969–present; Chairman, National Institute of General Medical Sciences Pharmacology-Toxicology Review Committee, 1967–69; member, graduate council, George Washington University, 1962–present; editorial board, Proceedings of the Society for Experimental Biology and Medicine, 1962–65; lecturer in physiology, Medical School, George Washington University, 1958–62; Meritorious Service Medal; Distinguished Service Medal; Dr. Rall has authored and coauthored over 100 published papers relating to comparative pharmacology, cancer chemotherapy, blood-brain barrier, blood CSF barrier, pesticide toxicology, and drug research and regulation.

Mr. FLOOD. Do you have some people with you that you would like us to meet?

Dr. RALL. Yes, indeed. Let me introduce Mr. George Kingman, our executive officer and a person new in that position, Mrs. Peggy J. McKinney, budget analyst.

Mr. FLOOD. Fine. Now you have a prepared statement, Doctor. How do you want to handle this?

Dr. RALL. I would like to read it, if I might, sir.

Mr. FLOOD. Fine, go ahead.

Dr. RALL. Mr. Chairman and members of the committee: It is a pleasure to appear before you again on behalf of the National Institute of Environmental Health Sciences to discuss our budget request for the coming year.

INSTITUTE MISSION

In the year since I last met with you, our country has been faced with deepening problems relating to recession, inflation, and the energy crisis. The energy dilemma, in particular, illustrates the importance of the NIEHS mission: that of developing new knowledge through research to protect us from the introduction into the environment—or continued use—of those environmental agents which are health hazards. This knowledge is used to guide regulatory action and to serve as the foundation for preventive and therapeutic programs.

Last winter, the Arab embargo on oil exports to the United States forced us to face the fragile nature of our dependence upon oil as a primary energy source. While adding impetus to our search for alternative sources, it also made us realize anew that solutions for the long-range energy problems may bring in their wake air, water, and other pollution problems. Thus, it is imperative that we evaluate potential effects—including the health impact—of the wide array of available energy options before we become totally committed to particular choices.

NIEHS has a clear role in evaluation of health effects of alternative energy sources. Since its establishment in 1966, NIEHS has developed a strong core program in basic environmental health research. This program capability can be brought to bear on a variety of problems that develop. Thus, there already was an organization in place that

could be turned to for assistance in establishing the public health aspects of the energy crisis.

We now can build on this core program so that in a relatively short period of time we will be able to develop health effects research programs designed to help provide assurance that the various technologies—currently in use, and proposed for development—for the production of energy can be implemented safely. This means that public and private capital will not be wasted on the development and implementation of energy systems that ultimately might be found to be unreasonably hazardous.

Historically, the major output of environmental health research has been closely allied to empiric toxicity testing of a variety of compounds preferably before, but commonly after, man is known to have been exposed. Recent research findings are beginning to provide us the opportunity to stop the introduction of harmful compounds into our environment and, more importantly, to prevent disease.

Identifying harmful agents before they become a hazard would allow us to realize substantial economic gains, as well as enormous health benefits. It is much cheaper in the long run to stop the introduction of a hazardous agent than to later retrofit a solution to the problem caused by that agent. In addition, techniques devised to control the introduction of effluents into the environment can themselves result in emissions of new or transformed effluents with potential hazards to health.

It might be noted that had the proper toxicity studies of NTA—nitrilotriacetic acid, once the great white hope of the detergent industry as a replacement for phosphates—been initiated in 1968 or 1969, at a cost of perhaps $250,000, the Federal Treasury might well have been saved a multimillion dollar tax writeoff claimed by manufacturers who had tooled up to make NTA. In addition, proper toxicity studies beforehand would have reduced the public confusion and concern associated with the NTA episode.

ASBESTOS

Work done at one of our grant-supported Environmental Health Sciences Centers points out how useful it is to have done one's homework. For the past 5 years, NIEHS has supported basic research by scientists at Mount Sinai School of Medicine into asbestos hazards to the general public. When asbestos fibers were found in Lake Superior water in Duluth, all kinds of technical questions immediately were asked: how to find the fibers, how to identify them, what some of the human health implications are. We had some of the answers, and we knew how to look at the problem.

Thus, when Congress added $1 million to our budget request for 1975 and directed us to initiate a long-term study on the effects of ingested asbestos, we could immediately respond. The DHEW Committee to Coordinate Toxicology and Related Programs—on which I serve as chairman—had previously established a subcommittee on asbestos protocol to develop scientific research protocols. In early February of this year, the subcommittee and our Institute convened an open meeting to discuss a working-draft potocol. Following this meet-

ing, NIEHS developed requests for contract proposals. Plans now are being made to award two contracts to study the health effects of ingested asbestos. One is a lifetime ingestion study in rats and will utilize four specific asbestiform types; the other is a lifetime ingestion study in hamsters and will utilize two or three specific asbestiform types.

Other aspects of the asbestos problem also have demanded our attention. Evidence is mounting from additional work being done at the Mount Sinai Center that far less than the intense exposure of the work environment is capable of producing asbestos-related disease. For the last two decades, Dr. Irving Selikoff—director of the Mount Sinai Center—and his team have been studying the men who produced asbestos insulation at a Paterson, N.J., plant from 1941 to 1954. Now the Mount Sinai team is studying the fate of those who lived with the Paterson workers.

Today, some 20 to 30 years after the workers' exposure, many wives, children, and other persons who were in contact with these men at home are beginning to show the effects of their peripheral and often brief exposure to this insidious material. Thus far, of 210 family contacts examined, nearly 40 percent were found by X-ray to have the kinds of abnormalities in their lungs common to asbestos workers. In some cases where X-ray abnormalities were found in the family, the worker had been at the Paterson plant for only a few days.

The new evidence raises questions not only about the adequacy of regulations designed to protect asbestos workers, but also about the hazards the general public may face from exposure to asbestos fibers.

DIETHYLSTILBESTROL (DES)

Other NIEHS scientists are working on the development of fast, reliable tests that can prevent another mass tragedy like thalidomide, which resulted in hundreds of babies born with undeveloped limbs. On the long road to this goal, they are looking in detail at the effects of environmental agents on reproduction and development. The still controversial diethylstilbestrol (DES), an additive for animal feed to speed up weight gain, is one focus of their studies.

In the early 1950's a number of women having trouble with their pregnancies were given DES to keep them from aborting. The daughters born to those women now have been found to have a far greater than normal chance of developing a rare vaginal tumor. Exactly how and when the damage occurred is not yet known. Our scientists are trying to find out.

In animal studies they have found that—at certain dose levels—all of the female offspring of DES-treated mother mice are sterile and, more surprisingly, that 60 percent of the males are premanently sterile. Although only vaginal tumors have been reported clinically, these studies suggest that reproductive tract lesions could be produced in the male offspring following DES exposure during gestation. This raises the possibility that DES may affect the same embryonic tissue in both male and female fetuses.

Our scientists have developed a mouse model of the DES toxic effect to explore how the unborn and newborn handle DES. This model is useful for studying factors associated with reproductive toxicity and transplacental carcinogenesis, and it hopefully will lead to

the development of predictive indicators of these manifestations of toxicity.

MARINE BIOMEDICAL RESEARCH

Implicit in NIEH's mission to develop knowledge of how environmental agents exert their effects on man is the goal of developing or improving approaches useful for solving environmental health problems. One such approach involves the use of marine organisms for biomedical research.

Many environmental health problems either arise from the sea or result in adverse effects on the ecology of the oceans. In addition, the sea is the ultimate receptacle for most environmental pollutants. Once pollutants enter the marine environment, they frequently are taken up by marine species and can enter the food chain at highly concentrated levels. Because these species often are important components of the human diet and could serve as sources of toxic human exposure to chemicals, we must know how marine life handles these various agents and their interactions. This is particularly important as marine species likely will be increasingly exposed to toxic components of oil as we place increased emphasis on energy production. We also need to know which organisms will store which poisons so we can avoid future problems like the Minamata disaster in Japan or the sword fish-mercury scare in our own country.

Another important reason for studying marine species is that they frequently are particularly sensitive to pollutants. So they often can be used to foreshadow a human environmental hazard and to provide a useful experimental model for human disease. By studying the effect of a pollutant on the affected marine species, we are able to get advance information on possible human health effects.

To date, NIEHS scientists have been concerned with studies on the accumulation by marine species of such pollutants as polychlorinated biphenyls or PCBs—a class of industrial chemicals that contaminate this country's waterways. They have found that PCB clearance from the lobster, flounder, and dogfish depends on the ability of the organisms to metabolize or alter it. Most PCB accumulation occurs in fat or fatty organs. Additionally, warm water and cold water fish apppear to differ in their ability to get rid of such pollutants. So where seafood comes from—warm or cold water—may determine the level of pollutant in its tissues, assuming the same amount of pollution in both cold and warm water.

Other work is beginning on the respiratory effects of the "Red Tide" organism, a marine organism that plagues the Florida coast and other coastal areas at certain times of the year. It kills thousands of fish and can be toxic to those who eat shellfish. It also is believed to adversely affect individuals with respiratory conditions, such as asthma and emphysema. Our scientists will use an improved isolated lung perfusion system developed at the Institute and different methods of aerosolizing to see what role particles, as opposed to the "Red Tide" toxin, play in the lung irritation seen in individuals.

Finally, because we believe marine biomedical research is an untapped national resource, on February 13–14 of this year we convened a meeting of directors of marine biological laboratories from throughout the country, as well as interested Government officials. Our goals

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were to establish baseline information regarding the current status of the laboratories and to explore opportunities for advancement of biomedical research. We wanted to identify those groups most able to help in assessing environmental health hazards or in the use of marine species as early warning systems for human hazards.

ISOLATED LUNG PERFUSION SYSTEM

In my discussion of the "Red Tide" toxin, I briefly mentioned the isolated lung perfusion system, a technique developed by NIEHS scientists. This system allows us to study rat and rabbit lungs outside the body while they are functioning normally. It keeps the lung "alive" in the sense that it operates as it does in the body.

Our interest in lung studies relates to the fact that not only is the lung the principal initial receptacle for some of the most hazardous pollutants in our environment, but also it stores substances that make a big difference in how the body handles foreign chemicals. Therefore, we need to know more about how the lung works so we can develop ways to predict how certain substances will be handled by the body. We would like to be able to take a chemical and predict how the body would absorb it, how it would be stored, and how long it would stay in the body.

At this time, we are looking at what happens in the lung to a special class of chlorinated hydrocarbons—including aldrin and dieldrin—related to the pesticide DDT. We are trying to learn which substances are more dangerous and which the body can handle. So far, it appears that the compounds with more chloro groups—those containing chlorine—are the ones the body stores. The compounds with few chloro groups appear to go through the body and are excreted rapidly. Additionally, extensive studies with the isolated lung perfusion system have shown that storage of aldrin or dieldrin in the lung is a passive process and that dieldrin does not become bound to the lung. Thus, once exposure stops, lung stores of aldrin and dieldrin flush out without leaving residues. Lung damage by these pesticides is, therefore, unlikely if exposures can be terminated.

The lung perfusion system is particularly important in this work because it enables us to make certain the effects measured are all happening in the lung. Because the blood carries foreign substances both from and to the lung, and some substances are changed in other organs and tissues into less harmless forms, we need to know how foreign chemicals get into the lung itself and how the lung alone handles them. In this way, we may be able to find the keys to help those people with lung problems.

SHORT-TERM TESTS FOR PRESUMPTIVE MUTAGENIC ACTIVITY IN MAN

During the past year concern over the development of cancer among workers exposed to vinyl chloride has emphasized our need for better ways to evaluate the potential hazard of such agents prior to exposure. In this area NIEHS scientists have made significant advances—particularly in developing short-term qualitative tests for mutagens, or agents that cause genetic damage. Genetic damage may take many forms. It may result, for example, in chromosome alterations that can cause spontaneous abortions or in an increase in inheritable diseases such as hemophilia or sickle cell anemia. These newly-developed tests

provide a practical solution to the problem of how to test the thousands of man-made chemicals already in the environment that have never before been tested. Our scientists also have made a major breakthrough in in vitro techniques for metabolic activation so we now can test the original compound and its mammalian metabolites, or those chemical derivatives accumulated by the body itself. Thus, we are able to avoid the necessity of using whole animals for screening and can reserve this capability for obtaining the quantitative data required for risk evaluation. These short-term tests are widely regarded as a sensitive initial method of quickly and cheaply screening chemicals and consumer products for possible toxic effects, and of singling out suspect compounds for more detailed evaluation in higher organisms. This capability is particularly important as exploratory testing of environmental chemicals is turning up new examples of mutagenetic activity in products in widespread use.

These tests also may offer answers in another area of concern. While the relationship between mutagenicity and carcinogenicity (cancer-causing ability) is still a matter of considerable scientific controversy, contract work—supported by NCI and developed with NIEHS assistance—is clearly showing a high correlation between the two types of activity. Thus, the newly developed short-term tests with microbes in combination with in vitro metabolic activation techniques appear to offer a means of detecting potential mutagenic and carcinogenic effects in man. This new technology also offers an approach for singling out from the thousands of untested chemicals in our environment those requiring more detailed testing in higher organisms. Until now we have not been able to effectively establish priorities based upon projected public health hazard.

The short term tests offer a potential solution to an additional problem faced by our major industries—namely, providing a testing capability for detection of adverse toxicological effects that can be used in early phases of product development. Too often various industries have invested considerable time and resources only to find out that a valuable product is carcinogenic in the traditional 2-year assay on laboratory animals. The utilization of short-term tests for mutagenicity offers a rapid, inexpensive mechanism for weeding out products with potential adverse effects early in product development. Our Institute plans to support additional research to make these short-term tests even more comprehensive and with an even higher degree of predictability.

One example of the capability of this approach relates to a compound I mentioned last year—AF–2, the nitrofuran derivative widely used as a food preservative in Japan since 1965. AF–2 was first determined to be mutagenic in the newly-developed short-term tests about 9 to 12 months ago. Much later it was found to be carcinogenic in mice. As a result, it now has been eliminated from food preservatives in Japan. In this connection, it is of interest that vinyl chloride is genetically active in these short-term tests. And it is interesting to speculate that had this genetic activity been determined years ago, this hazard to our industrial workers and population in general might have been avoided.

The finding that vinyl chloride is genetically active in these tests well illustrates the fact that we must develop better methods to deter-

mine the effects of exposure to genetically active chemicals on man himself. In addition, we also must determine if compounds structurally similar to vinyl chloride are genetically active in these tests and, if so, what the effects of exposure to such compounds are. Currently, we are beginning preliminary investigations on vinyl bromide—a compound structurally similar to vinyl chloride—which is used to make flame resistant fabric. Because this fabric can save lives, we must determine if vinyl bromide may be highly toxic.

The difficulty with a situation such as the discovery that AF–2 is a potential mutagen and carcinogen is our inability to evaluate the immediate and long-term effects of such exposure directly on man. Although the genetic basis of many human diseases is well established, we are extremely limited in our ability to determine the immediate effects of genetic damage, and an increase in cancer would not be expected for 15 to 20 years. Thus, in such situations we may have the illusion of safety based on our inability to test, rather than on sound scientific data. It is, therefore, urgent that we develop a capability to perform meaningful tests on man himself to determine and evaluate the effects of inadvertent exposure to environmental compounds.

This urgency is magnified by the recent discovery that almost all commercially available hair dyes are genetically active in the newly-developed short-term tests. We do not know whether these dyes also are potential carcinogens. Thus, we need to evaluate the risk to an estimated 20 million people in this country alone who dye their hair. NIEHS already has initiated studies to see whether hair dyes do cause genetic damage in other experimental organisms in order to better evaluate the risk for man. We plan, in addition, to continue to develop our program in environmental mutagenesis-carcinogenesis to further validate the short-term tests for use in mass screening programs.

SUMMARY

Mr. Chairman, I am very pleased to have had the opportunity to tell you of our progress and concerns over the past year. We believe the coming year will be a challenging one by providing us more opportunities to contribute to the growing field of environmental health research. I am certain the NIEHS will strive to meet the challenge and to provide this country the science base of health knowledge needed to protect each of us.

In conclusion, Mr. Chairman, the budget request for the National Institute of Environmental Health Sciences for 1976 is $31,113,000. I shall be pleased to try to answer any questions and supply additional information desired for the record.

IMPACT OF REDUCTION

Mr. FLOOD. Doctor, your budget proposes a reduction of $3,824,000. What is the impact of such a reduction on your research activities?

Dr. RALL. It will force us to go at a somewhat slower pace than we were able to go at this current year.

Mr. FLOOD. You will be able to fund all of your noncompeting continuation grants?

Dr. RALL. No; we will not be able to fund all of them.

Mr. FLOOD. How much more do you need?

Dr. RALL. To fund those noncompeting grants and contracts we will need $5.5 million.

Mr. FLOOD. If we were to restore your budget to the 1975 level, how many new grants will you be able to fund?

Dr. RALL. If we were restored to the same level of program operation, it would require an additional $10.9 million over the President's budget. This would provide noncompeting requirements and the same level of competing as funded in 1975. This would include 63 competing research grants, 4 new research career development awards, 16 new individual and institutional awards, and 10 new research contracts.

Mr. FLOOD. Would you put the entire increase in new grant research?

Dr. RALL. No; we would prefer to honor our moral commitments to continue the work throughout the period of these grants as they were awarded.

Mr. FLOOD. Why wouldn't you put the entire increase into research grants?

Dr. RALL. We feel that we should also honor our previous commitments in fellowships, training, and contracts as well.

Mr. FLOOD. In which of your programs would you invest this increase in funds?

Dr. RALL. We think we would probably spread it with emphasis on the mutagenic short-term testing program.

RESEARCH CAREER DEVELOPMENT AWARDS

Mr. FLOOD. Looking at page 182 of your justifications you state, "Three lower priority noncompeting research career development awards will not be funded in 1976." Will you tell the committee what is a research career development award?

Dr. RALL. These are 5-year awards given to young scientists, perhaps 5 or 10 years after their doctoral degree to allow them to devote a major amount of their effort to research itself and not to be concerned in a school by having too great a teaching load or too many committees. This gives them a chance to develop their research career to their best.

Mr. FLOOD. How do you determine which of your research career grants are of low priority?

Dr. RALL. That is always a very difficult decision.

Mr. FLOOD. There is no doubt about that.

Dr. RALL. We simply tried to determine which ones seemed to us to have less national importance in the research they were doing.

Mr. FLOOD. What kind of yardsticks do you use for that? How do you do that?

Dr. RALL. The sort of things that we think are terribly important in environmental health research are the sorts of short term testing I was talking about. This is the first priority. In addition, of course, we had the information from the review groups on their evaluation of these candidates and the priority scores. We also used that in determining which to terminate.

DECREASE IN RESEARCH CONTRACTS

Mr. FLOOD. Now on page 182 you show a decrease of $1,074,000 for five research contracts that will not be funded in 1976. Now, did those contractors complete their work under the contract? Are you just simply cutting them off right in midstream?

Dr. RALL. I am afraid it is the latter suggestion. This will in fact include the asbestos contract that I described in my opening statement.

Mr. FLOOD. Can you tell us what kind of work you are now carrying on under these five research contracts?

Dr. RALL. Well, many of our research contracts are involved in developing short-term testing that I described in the opening statement, getting highly developed strains of mice where we can look for mutagenic events, developing chemical systems for studying the blood of either mice or man to determine mutagenic events.

ALTERNATE ENERGY SOURCES

Mr. FLOOD. You stated that your Institute has a clear role in evaluation of the health effects of alternate energy resources.

Will you outline for the committee your efforts in that area?

Dr. RALL. There are two problems here. We are concerned, in addition to the alternate energy sources, about more of the same old pollutants. We are very concerned about the problems of sulfur oxide in the air. Some of the new sources, shale oil, oil and gasification, may well also increase SO_2 problems. The problems with shale oil and coal and oil gasification which I think are the near term alternates that we can look forward to are the release into the environment, not only of the oil pollutants but of many new, high mutagenic and carcinogenic complex organic compounds.

Mr. FLOOD. I have some concern about the matter of gasification or liquefication.

In the hard coal for years and years we have been doing gasification. We can do a great deal of it. The only reason we do not know it is because so far natural gas has been so cheap and the overhead costs of setting up a physical facility to do gasification is astronomical. That is why we have not done it. We have two or three plants that have been doing it for 2 or 3 years in a small way. So you are faced right now with quite a problem because of the energy crisis.

Dr. RALL. Yes, with the price of oil going up.

Mr. FLOOD. It is no longer talk or research. We want to move tomorrow on gasification.

Dr. RALL. There are some problems with gasification in some of the techniques used not in Pennsylvania but in West Virginia.

Mr. FLOOD. That is the soft coal people. That is a special problem, more of a problem.

Dr. RALL. Yes.

HEALTH EFFECTS OF SULFUR OXIDE

Mr. FLOOD. I understand you submitted a report to the Office of Management and Budget recommending a program of research studies designed to develop information on the health effects of sulfur oxide.

Dr. RALL. That is right.

Mr. FLOOD. Will you be able to conduct this study with your 1976 budget?

Dr. RALL. The major study that we proposed to do was to follow——

Mr. FLOOD. Will you be able to do it?

Dr. RALL. No, sir.

Mr. FLOOD. Will you submit for the record a copy of your report to the OMB on the sulfur oxide?

Dr. RALL. Yes.

[The information follows:]

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Review of the Health Effects of Sulfur Oxides

Submitted by David P. Rall*

The pollution in the air is a complex mixture of chemical substances of varying toxicity of which the sulfur oxides are a principal component. Those components which pose the primary hazards to human health have not yet been fully identified, nor have their respective contributions to human disease been fully determined. Efficient and effective control strategies are dependent upon the identification and understanding of these toxic components. Ultimately, the goal of standard-setting should be the development of composite pollution indices rather than control of individual pollutants.

Concentrations of SO_2 in the ambient air twice the current standards are associated with adverse health effects. A considerable body of evidence suggests that there may be discernible human health effects from exposure to concentrations approximating the current standards. There is therefore no basis for relaxation of the present standards for sulfur oxides at this time. Since the scientific basis for this judgment is incomplete, further scientific information will be required either to validate the present standards or to justify alteration of these standards.

Review of Health Effects of Sulfur Oxides

Background and Objectives of the Study

Mr. Roy Ash, Director of the Office of Management and Budget, requested the Department of Health, Education, and Welfare to take the lead in a cooperative study with the Environmental Protection Agency to examine the existing scientific information on the health effects of sulfur oxides in the ambient air. Specifically, Mr. Ash asked:

> "We are particularly interested in an assessment of the adequacy of current information on the ambient levels of sulfur oxides to ascertain the extent to which human health is affected. If a definitive statement cannot be provided on the basis of current information an outline of the types of studies necessary to provide a definitive level should be developed. Assuming that additional studies may be necessary, we would appreciate receiving an estimate of the time required and costs to complete the additional studies."

A report on the following specific areas was requested: (1) the extent of the demonstration of a cause-and-effect relationship between exposure to sulfur oxides and adverse health consequences, including the issue of dose-effect relationships; (2) the degree to which these findings are supported by epidemiologic, clinical,

*This report is the result of a study group chaired by Dr. David Rall, NIEHS, P.O. Box 12233, Research Triangle Park, N.C. 27709. Dr. Myron Mehlman, Office of the Assistant Secretary for Health, Department of Health, Education, and Welfare, served as executive secretary; Dr. Roger Glass, NIEHS, was staff [illegible]; Dr. John Finklea, Environmental Protection Agency, was liaison representative. Drs. Bernard Goldstein and Norton Nelson authored the section on Atmospheric Chemistry; Dr. Richard L. Riley authored the section on Toxicology; and Dr. Ian T. Higgens authored the section on Epidemiology.

and experimental or laboratory studies, including matters of agreement or disagreement among the findings produced by the various study approaches; (3) the variable susceptibility to adverse effects of sulfur oxides among different population groups; (4) a quantification of health effects in relation to various levels of exposure; and (5) the relationship between various levels of sulfur oxide exposure and costs in terms of impaired health, including the costs of care and loss of productivity among those who are or may be adversely affected by exposure to sulfur oxides.

This study has examined the existing scientific information and answered, insofar as is possible, these important questions. It is clear that additional information on the health effects of sulfur oxides is urgently needed. A program of research studies designed to develop such information is therefore included.

Summary of Available Information

The chemical form of sulfur oxides in the ambient air which is associated in epidemiological studies with morbidity and mortality has not yet been clearly identified. The sulfur-containing products which have been implicated include SO_2, sulfuric acid, and inorganic sulfates. SO_2 gas is generated primarily by the process of burning fossil fuels containing sulfur. SO_2 remains in the ambient air for 1–7 days, during which time it can be converted to sulfates and sulfuric acid by sunlight, photochemical oxidants, or by the catalytic effect of certain particulates in the air. These processes are complex and not quantitatively understood. SO_2 in the ambient air therefore provides a reservoir from which the more toxic sulfates and sulfuric acid derive. On a nationwide basis, the average ambient air concentrations of SO_2 have been decreasing in the last few years because fossil fuels with a lower sulfur content have been used. The concentration of suspended sulfates in the air has not correspondingly decreased since 1963 and appears to be highest over the northeast section of the nation.

Studies on laboratory animals and human volunteers have shown that inhalation of SO_2 alone does not affect lung function at concentrations 10 to 100 times that commonly found in ambient air. Mixtures of SO_2 and particles are often more toxic than SO_2 alone, the toxicity depending on the SO_2 concentration, the nature and size of the particles, and the ambient relative humidity. Particles can absorb SO_2 and facilitate its reactions. Airborne particulate metals (vanadium, manganese, iron, etc.) catalyze the conversion of SO_2 to sulfuric acid and sulfates. Sulfuric acid and acid sulfates have proved to be particularly toxic in animal experiments.

Studies in animals are helpful in determining mechanisms of action in the body, but are not suitable for establishing safe levels for human exposure. The number of animals tested has been small relative to the human population at risk daily. The animals are selected to be healthy, vigorous, and young whereas the humans most susceptible to pollutant effects are the diseased, very young, or aged.

For estimates of safe levels, we must turn to epidemiologic studies which relate environmental factors including pollution to states of health or disease.

Health effects may range from discomfort through physiological deviations from the norm, prevalence of symptoms, appearance of illness, lost working time, and premature retirement to complete incapacity and death. In practice, it is better to consider these indices in the reverse order, starting with death, serious illness, and significant disability, about which there can be little argument, and to proceed thence to physiological deviations and minor disorders, the significance of which may be open to question. Disease and death seldom, if ever, result from pollution alone. They are the outcome of many factors, both individual and environmental, acting together. Any epidemiological study of the effects of air pollution must allow adequately for these other factors. Indeed, the quality of such studies often depends on the success with which such allowance has been achieved. At the other end of the range of health effects, the implication of minor symptoms and small deviations from some physiological or biochemical norm between persons living in polluted and nonpolluted neighborhoods may be imperfectly known. Until it can be shown that such effects predispose to disease, disability, or reduced expectation of life, the weight that should be given to them in setting standards

will remain a matter for personal judgment.

Acute episodes of high pollution have clearly resulted in mortality and morbidity. Often the effects of high pollutant concentrations in these episodes have been combined with other environmental features such as low temperatures or epidemic diseases (influenza) which may in themselves have serious or fatal consequences. This has sometimes made it difficult to determine to what extent pollution and temperature extremes are responsible for the effects. Nevertheless, there is now no longer any doubt that high levels of pollution sustained for periods of days can kill. Those aged 45 and over with chronic diseases, particularly of the lungs or heart, seem to be predominantly affected. In addition to these acute episodes, pollutants can attain daily levels which have been shown to have serious consequences to city dwellers. For many years in London, daily deaths and illnesses were clearly related to daily levels of smoke and SO_2. Comparable observations have been made in New York City, Philadelphia, and Chicago. In the New York–New Jersey Metropolitan area, an analysis of daily mortality for the years 1962–66 showed that deaths were 1.5% below expectation at the lowest SO_2 concentrations and 2% above expectation at concentrations of 500 $\mu g/m^3$ and above. A similar though weaker relationship was found in Philadelphia but not in Chicago. This work urgently needs to be pursued, since it calls into question the concept of a no-effect level on which present air quality standards are based.

The implication of daily levels of SO_2 and particulates has been studied in particularly vulnerable groups, such as patients with chronic bronchitis and emphysema. Deterioration in their respiratory well being has resulted from a daily concentration of SO_2 of about 500 $\mu g/m^3$ which is not much above the 24-hr primary standard. A few studies have even suggested that deterioration in particularly vulnerable groups may occur with daily concentrations which are below this standard. Confirmation of this is urgently needed.

There is a large and increasing body of evidence that significant health effects are produced by long-term exposures to air pollutants. Acute respiratory infections in children, chronic respiratory diseases in adults, and decreased levels of ventilatory lung function in both children and adults have been found to be related to concentrations of SO_2 and particulates, after apparently sufficient allowance has been made for such confounding variable as smoking and socioeconomic circumstances.

It is not possible to state a concentration below which such health effects will not occur. In many studies the proportion of persons affected increases from the lowest to highest categories of pollution. Had even lower categories of pollution been used in the analyses, even lower critical levels might have been suggested.

Thus, as in the case of daily mortality, the concept of no-effect level may be a chimera. A reasonable conclusion from these studies would however be that health effects have been found when annual levels of particulates or SO_2 exceed 100 $\mu g/m^3$. The primary SO_2 annual level thus appears to be low enough but not excessively low.

The need for more information about the lowest levels of pollution which might produce significant effects was recognized by the Environmental Protection Agency through the Community Health and Environmental Surveillance System (CHESS) studies. The CHESS studies were intended to provide this information. These studies were also intended to monitor any changes in health which might occur as a result of any change in pollution concentrations. It is probably safe to say that, in attempting to provide a large amount of information as quickly as possible, the CHESS studies have as yet been less effective than they might have been had a more deliberate approach been adopted. Any defects in design, methods, and execution of these studies, however, can be remedied for the future. The importance of the monitoring aspects of this program can hardly be exaggerated. It is essential that the technique of monitoring be impeccable. Present assessment of the CHESS studies is that they do not in themselves justify and change in the standards. The CHESS studies also provide some support for the viewpoint that acid sulfates and sulfuric acid may be more important pollutants than SO_2 in terms of their health consequences. Further information on this is urgent. In particular, better evidence is needed to suggest an appro-

priate standard for sulfates. There is some evidence that local controls of SO_2 (by higher stacks, etc.) is leading to a wider dissemination of particulate sulfates. All this is resulting in a rather uniform level of sulfates in the northeast United States. Should sulfate concentrations rise uniformly over a wide area, it might be impossible to find any appropriate low sulfate control areas with which any putative health effects should be compared.

Catalytic converters which are to be installed on automobiles to control pollution may become a new source of increased sulfates and sulfuric mist in the breathing zone of urban areas. This may pose potentially severe problems in areas saturated with automobile use. The exhaust from cars with catalytic converters contributes only a small portion of the atmospheric sulfate, but this may be disproportionately significant because it occurs in the breathing zone of a large portion of the urban population.

Summary of Key Problems

The first problem concerns the identification and isolation of the ultimately toxic pollutant(s). SO_2 has often been used as an index of pollution and is sometimes considered a main pollutant. SO_2 alone is of relatively low toxicity, but in the presence of other pollutants, such as total suspended particulates (TSP) or ozone, or after conversion to particulate sulfate or sulfuric acid, it can become a major contributor to adverse health effects. Yet SO_2 and TSP (of which sulfates are a variable fraction) are the measured pollutants to which controls are directed. Operationally, to prevent the health consequences of SO_2-related pollution, we must know more of the interrelationships between these sulfur oxides, the effects of particle size, the importance of particulate composition, the synergistic toxicity between SO_2, particles, and humidity, and the adverse health effects of suspended sulfates and sulfuric acid mist.

Further studies are crucial for sound policy. It is possible that a policy decision to reduce SO_2 alone without control of particulates could well lower our SO_2 pollution index but yield no benefits for health. Likewise, an attempt to clean the air of particulate matter without controlling SO_2 might preferentially clean up the more manageable large particles and effect a marked improvement in the TSP index while leaving the smaller, more toxic respirable-sized particles for man to breathe. We must aggressively seek a broader and firmer scientific foundation on which to base present and future policies. These policies will affect billion dollar decisions and involve the health and well being of millions of Americans. In the area of air pollution policy, inertia and inactivity without research support is in itself a multibillion dollar decision.

The second problem concerns the importance of epidemiologic data in arriving at a primary ambient standard. While we may review the present air criteria levels many times and underscore the incomplete data base, we must also realize that epidemiologic evidence will be central to any future reevaluation of the present standards. These studies require years to complete land demand continued support over long periods of time.

In this regard, the continuing results of the CHESS studies will be of great assistance in improving our estimate of a no-effect level for SO_2. The community of epidemiologists and scientists outside EPA is not adequately familiar with the details of these very extensive studies to endorse or challenge the reported results. In the normal course of scientific investigation, review, and publication, such understanding and acceptance or rejection would occur. This process however would take years, and the answers are needed now.

It would be important for EPA to assemble a group of academic and government epidemiologists to provide in-depth review of the mass of data from this ongoing program and offer continuing advice. Furthermore, consideration should be given to having complementary studies performed by extramural organizations.

In the near future, pollution levels will fall in some areas and may rise in other areas if high sulfur fuel must again be burned. Our understanding of the effects of pollution on health could be significantly advanced if epidemiologists with foresight and funding could set up studies now of the temporal consequences on the health of the exposed populations of these unplanned experiments.

Both of these approaches to setting air quality

criteria involve the input of well trained chronic disease epidemiologists, a commodity which is in short supply within the American medical community.

The third problem concerns the generally inadequate data base upon which these standards rest. These standards will affect the lives and health of millions of people and influence the expenditure of billions of dollars. The bulk of the laboratory animal studies which have delineated the synergistic toxicity of SO_2 and certain particles has been performed in a single laboratory over the last two decades and cost in the aggregate, approximately $600,000. It is fortunate that this single investigator did not choose another research topic 20 years ago.

When the research data base for standard setting is inadequate and the margins of error are large, prudence dictates a conservative approach. Standards will be set at more stringent levels to insure that the public health is protected. More information can decrease the margins of error and result in more realistic perhaps less stringent standards.

The range of uncertainty in the study of the adverse health effects of SO_2 and particulates has been quantified in the CHESS reports as the "worst" and "least" case examples. The potential risk of a wrong decision includes: (1) accepting the lowest levels (worst case) to be significant to health when this is not true and consequently wrongly promoting expensive pollution controls, or (2) accepting the highest levels (least case) to be significant when this is not true and consequently wrongly allowing many people to suffer the ill effects of pollution toxicity. In our uncertainty rests a multibillion dollar decision which could have potentially disastrous consequences for future Americans. Our need to make this decision on a more secure scientific basis is imperative.

Answers to Specific Questions Posed by the Office of Management and Budget

(1) Cause-and-Effect Relationship between Exposure to Sulfur Oxides and Adverse Health Consequences: Cause-and-effect relationships probably exist at ambient air concentrations of sulfur oxides somewhat above the current standards in the United States today, perhaps at twice the current standards. Some studies suggest these relationships also exist at concentrations in the range of the primary ambient air standards for SO_2 and TSP. Tentative exposure–effect relationships are available, but must be treated as suggestive, not definitive.

(2) Agreement with Epidemiologic, Clinical, and Experimental or Laboratory Studies: The clinical, laboratory, and experimental studies at relatively high concentrations of sulfur oxides in the ambient air are consistent with the current epidemiologic data. Information is not available to provide the desired level of confidence at concentrations approximating the current standards. This can be corrected by the fuller development of the needed information.

(3) Susceptibility to Adverse Effects of Sulfur Oxides of Different Population Groups: The population groups of particular concern are young children, the elderly, and any persons with pre-existing diseases of the heart and lungs.

(4) Health Effects at Various Exposure Levels: The purpose of many epidemiologic studies is to define an exposure–response relationship. The best available tentative exposure–response curve is presented in Figure 1. An imaginative attempt to group the

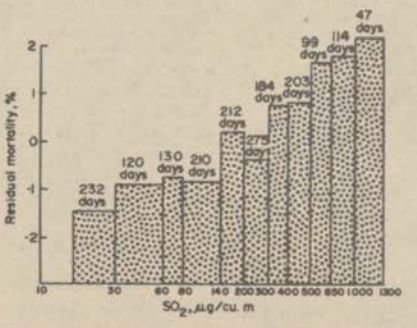

FIGURE 1. Dose–response curve for SO_2. Means of residual mortality by SO_2 class in New York-New Jersey metropolitan area, 1962–1966 (1826 total days). Data of Buechley *(1)*.

graded health consequences of exposure to SO_2 against a composite index is illustrated in Figures 2 and 3.

(5) Relationship Between Sulfur Oxides Exposure and Costs in Terms of Impaired Health: We are not convinced that there are currently available reliable estimates of the number of people affected by SO_2. A cost estimate is given in Table 1, but we are not convinced of the validity of the methods used to derive these figures.

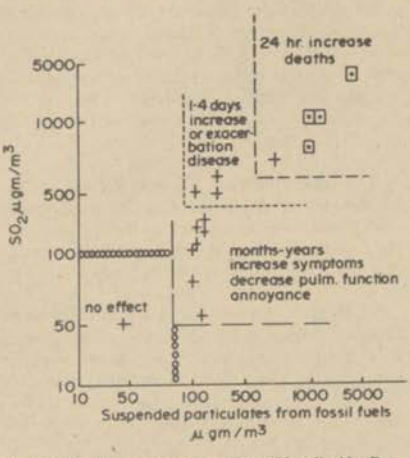

FIGURE 2. Dose—response curve for sulfur dioxide. Data of Dr. Benjamin Ferris (personal communication).

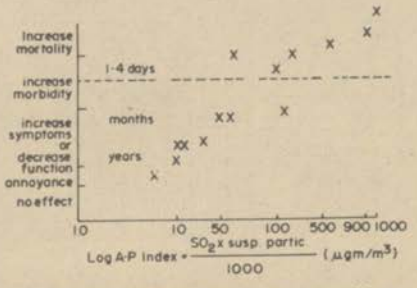

FIGURE 3. Dose—response curve for total suspended particulates. Data of Dr. Benjamin Ferris (personal communication).

Table 1. Estimates of the cost of the health consequences of air pollution.

Study	Cost, $x10^{-9}$	Considerations
Waddell *(2)*	0.9–3.2	SO_2 effects on human health.
	1.6–7.6	Particulates + SO_2 combined effects on human health.
	7.1–20.1	All measurable adverse environmental effects
Lave *(3)*	7.0	Total health benefit that would accrue in 1978 based on 1970 dollars and 1969 data

Research Proposals Designed to Provide Needed Information on Health Effects of the Sulfur Oxides

Research efforts designed to develop needed information on the health effects of the sulfur oxides are outlined in Table 2.

Laboratory Research on and Monitoring for the Multiple Factors in Sulfur Oxide Toxicity: It is important to delineate which specific compounds in the mixture of present pollutants are ultimately damaging to pulmonary structure and function. It will be impossible to develop well designed and effective control programs until more information is available on (1) the toxicity of SO_2, various sulfates, and sulfuric acid mist and on (2) the conditions necessary for the interconversions of these sulfur oxides.

The proposed program (Table 2) includes monitoring, atmospheric chemistry research, and biomedical research.

Epidemiologic Research: Ultimately the development of proper cost effective ambient air standards depends on epidemiologic evidence. A number of steps should be taken to provide for this necessary epidemiological evidence. These are summarized in Table 3.

As circumstances develop, SO_2 levels may be projected to fall in some areas and to rise in others if return to high sulfur fuel becomes inevitable. Advantage should be taken of this situation by initiating a prospective study designed to document the health effects of

Table 2. Laboratory research on and monitoring of multiple factors in sulfur oxide toxicity.

Program	Estimated cost, $/yr	Duration, yr	Estimated time to achieve significant results, yr
A. Intensify study of qualitative and quantitative aspects of the interconversions between SO_x, suspended sulfates, and sulfuric acid mists; rates and routes of conversion and residence times of intermediates and end products are important	700,000	4	2
B. Develop and validate methods for monitoring suspended sulfates and sulfuric acid mist	400,000	2	2
C. Develop a national monitoring system for suspended sulfates and sulfuric acid mist	600,000–2,000,000		3
D. Maintain the present National Air Sampling Network and keep surveillance and quality control tied into the EPA Office of Research and Development	None		1
E. Continue the development of atmospheric air pollution	600,000	5	2
F. Investigate the pulmonary responses and toxicity in laboratory animals and in human volunteers of the various sulfur oxides under various conditions of humidity and specific particulates of differing size	2,000,000	4	3

Table 3. Program of epidemiologic research.

Program	Estimated cost, $/yr	Duration, yr	Estimated time to achieve significant results, yr
A. Study to document the health effects of variations in concentration of ambient sulfur dioxides	1,000,000 Lesser amounts	5 10	5
B. Studies by academic institutions	1,000,000	6	4
C. Strengthening of CHESS study by outside input and review	50,000 100,000	1 thereafter	1
D. Study of daily mortality rate in New York City			
1. Extend this study to present	300,000	1	1
2. Provide resources for the National Center for Health Statistics to maintain daily mortality data for future studies	40,000		1–2
3. Continue New York study on ongoing basis	150,000		2
4. Extend similar studies to three other cities	500,000		2
E. Design and fund a manpower training program to recruit more chronic disease epidemiologists	500,000	10	4–5

these changes. This study is of such a critical nature that a more detailed description is given in the following section.

In order to replicate certain of the very important studies encompassed in the CHESS program it would be useful to invite academic institutions to initiate studies in certain critical areas.

It is necessary to strengthen the CHESS study by providing the opportunity for extensive outside input and review. With such review the CHESS results will be increasingly important. (The estimates in Table 3 do not include funding for the CHESS program which should be continued.)

The study of the daily mortality rate in the New York City Metropolitan area as related to daily SO_2 concentrations has provided important information. This study was terminated in part because the National Center for Health Statistics stopped coding mortality on a daily basis. Extension of the study to the present (if SO_2 levels continue to fall) and to the future (if SO_2 levels rise) would be very important.

The continuing critical shortage of epidemiologists is a major impediment to further definition of the health effects of air pollution.

Every critical review of the relationship of environmental factors to health calls attention to the inadequacy of the quantity or quality of epidemiologic studies. One of the reasons for this is the serious shortage of qualified environmental epidemiologists. Most epidemiologists are oriented to the study of the infectious diseases; substantially different orientation and different skills are necessary for effective study of chronic noninfectious diseases. Sophisticated methods are required, which take into account not only the biologic characteristics of people (age, sex, race, genetic defects, etc.) but also the great variety of external or environmental factors which influence health and disease (social class, season, occupation, personal habits such as smoking and drinking, diet, place of residence, etc.).

Whereas some medical specialists have been trained in excess in recent years, this is not the case with this kind of epidemiologist. In fact, the opposite is true — among all medical specialities, this one is probably in shortest supply compared to need.

Training facilities for this type of epidemiologist are also very limited. There are a few training centers in schools of public health and medical schools but no center in the Federal government, in contrast to the outstanding facility operated at the Center for Disease Control for many years, for training of infectious disease epidemiologists.

Opportunities exist for increasing the number of epidemiologists by combining the resources of academic institutions and the Federal government. If funds were available, existing university centers could substantially increase trainees without much increase in faculty. The Federal government has resources for field training; for example, in several institutes of NIH, EPA, NIOSH, and the NCHS. Academic institutions and Federal agencies should work together to develop an integrated program. Opportunities for training should be open to college graduates and should not be limited to physicians, dentists, and veterinary physicians.

Research Proposal to Maximize Information on Human Health Effects from Projected Alterations of Concentrations of Ambient Sulfur Oxides: Review of the available information concerning the health effects of sulfur oxide air pollutants reveals significant deficiencies in the extent of knowledge available to base judgements concerning appropriate control strategies. In view of the current shortage of low sulfur fuels, a significant deterioration in regional air quality is expected to develop this winter and to be repeated for a number of years subsequently. Dr. Frank Speizer of Harvard University has submitted a preliminary outline of studies aimed at determining the health effects of increased ambient levels of sulfur oxides brought about by the reintroduction of high sulfur fossil fuels. The approach consists of epidemiological evaluation of the health of population groups who will be inevitably subjected to elevated ambient levels of sulfur oxides due to use of high sulfur fuel. Its goal is to provide information relevant to establishing appropriate standards and control strategies for sulfur oxides.

The studies are based on a number of assumptions which include the ability to forecast which parts of a definable geographic area will have the

worst air quality, the ability to obtain long-term commitments for large-scale cooperative studies from national, state, and local institutions, and the availability of sufficient numbers of trained personnel to perform the studies.

Studies of acute effects would focus on respiratory disease in cohorts of school children, normal adults, and high risk groups followed for up to five years. Evaluation of school children is envisioned to involve approximately 1000 subjects, age 9–12, divided into three groups depending upon exposure levels. Respiratory illnesses, school absences, and pulmonary function would be monitored. New groups of 9-year-olds would be added yearly in order to provide data on the cohort effect of changing levels of pollutants. The estimated cost would be $75,000–$100,000/yr per 1000 children.

Studies of normal adults would consist of identifying cohorts living in areas with the same pollution or cohorts receiving similar occupational exposures to dust who would be evaluated with repeated biennial assessment of respiratory symptoms, work days lost, hospitalization, etc., particularly during high exposure periods. Control groups would be from relatively unexposed areas. Cost per subject is envisioned to be in the same range as the study of children but more subjects will be needed due to the confounding effects of smoking.

The special risk groups to be studied would consist of "normal" (i.e., least detectable change) subjects who have been identified to have relatively decreased pulmonary function in a screening program, patients previously hospitalized for respiratory failure, and asthmatics of all ages. No cost estimates are given.

to evaluate whether these levels of sulfur oxides have real chronic effects would require follow-up of these cohorts for at least 10–15 yr beyond the initial acute studies described above. A formal registry system of this type appears feasible in school children and also may be practicable in other population groups.

Background Review: Atmospheric Chemistry

Sulfur oxides in the atmosphere can most conveniently be considered as occurring in three forms: sulfur dioxide (SO_2), sulfuric acid (H_2SO_4), and inorganic sulfates.

Sulfur dioxide is the anhydrous form of the weak acid, sulfurous acid (H_2SO_3). The salts of this acid are known as sulfites and bisulfites. These have not usually been searched for in the atmosphere as it is believed that essentially all sulfur dioxide is eventually oxidized to sulfates, either in air or following absorption by plants or adsorption on surfaces.

Sulfuric acid is the hydrated form of sulfur trioxide (SO_3), which is derived from the oxidation of sulfur dioxide. As sulfur trioxide is intensely hygroscopic, it is almost immediately converted into sulfuric acid in the atmosphere.

Inorganic sulfates are presumably derived from either the reaction of sulfuric acid with cations or by the oxidation of sulfites. There is little information available concerning the possible formation of organic sulfates in the atmosphere.

The major source of urban sulfur oxides is the combustion of fossil fuels in stationary sources. Approximately 98% of the sulfur released to the air is in the form of sulfur dioxide and most, if not all, of the remainder is sulfuric acid. Inorganic sulfates may also be discharged preformed in certain industrial effluents. It must be emphasized that while almost all of the sulfur dioxide produced by combustion of fossil fuel is eventually converted into sulfate, not all atmospheric sulfate is derived from this source. Natural sources of sulfur dioxide and hydrogen sulfide (H_2S) can be oxidized to sulfate. Aerosols of sea water are a direct source of atmospheric sulfate *(4, 5)*. While it has been estimated *(5)* that only one-third of the sulfur in the entire global atmosphere is derived from pollutant sources, this observation is not pertinent to local respirable ground levels of sulfur oxides which in urban areas are almost entirely derived from fossil fuel combustion.

The formation of sulfates from sulfur dioxide in the atmosphere may best be viewed as two separate, although perhaps related, chemical processes. The first is the oxidation of sulfur dioxide to sulfuric acid and the second is the reaction of sulfuric acid with cations to form sulfates. Sulfur dioxide in pure air is very slowly oxidized by sunlight to sulfuric acid with a rate of about 0.1%/hr *(6)*. While there is inadequate information to characterize fully the chemical processes by which sulfur dioxide is oxidized in polluted urban air, the conversion is much more rapid than in pure air. This is due to the pres-

ence of other air contaminants which in general greatly facilitate the oxidation of sulfur dioxide. Two processes appear to be involved: oxidation by components derived from photochemical processes *(7–12, 34)* and catalytic oxidation predominantly by certain types of particulate aerosols *(13–21)*. The photochemical reaction is associated with the action of sunlight on oxides of nitrogen and hydrocarbons derived primarily from mobile sources. The ensuing reactions result in the production of agents capable of oxidizing sulfur dioxide to sulfuric acid. As an illustration of the complexity of this process, the presence of sulfur dioxide in the photochemical mixture enhances aerosol formation thereby tending to decrease sunlight which in turn decreases the rate of photochemical reactions. Estimated rates for the oxidation of sulfur dioxide due to the photochemical process range as high as 18%/hr/(S. K. Friedlander, personal communication, Sept. 1973). Rate data are summarized in Table 4.

Catalytic oxidation of sulfur dioxide occurs in the absence of sunlight in aerosols on which sulfur dioxide has been adsorbed. Major research interest has focused on the catalytic role of metallic compounds in the aerosols including manganese, iron, vanadium, aluminum, lead, and copper. The total reaction is a highly complex process with many interrelated variables which are poorly characterized *(34)*. These include adsorption rate of sulfur dioxide, particle or droplet size, chemical composition, rate of diffusion of reactants within the aerosol and relative humidity. Relative humidity is a major determinant, as the reaction occurs in water droplets containing the metallic particulates and absorbed sulfur dioxide. Furthermore, as an acid pH decreases the rate of sulfur dioxide oxidation, the formation of sulfuric acid in the aerosol would tend to be self-limiting unless the acidity is diluted by additional water vapor. In this respect, alkaline metal compounds (e.g., iron oxide) and ammonia also enhance the reaction rate by decreasing droplet acidity through their buffering capacity. Extrapolated levels for the rate of oxidation of sulfur dioxide by catalytic processes in urban air range upwards of 2%/hr.

Weather has a great effect on these atmospheric chemical processes. Inversion levels will dictate the concentration of sulfur oxides and other contaminants thereby influencing the rate at which they react. Increased humidity accelerates catalytic oxidation of sulfur dioxide, while cloud cover might be expected to lower the rate of the photochemical process, and rain will wash out sulfur oxides from the atmosphere. Temperature affects reaction rates and the solubility of gases. Wind influences the rate, direction, and distance of dispersal.

The average residence time of sulfate in the atmosphere is probably measured in days. A large urban source of sulfur dioxide will therefore result in increased atmospheric sulfates being present many miles downwind. In regions where there are multiple urban sources of sulfur oxides, such as the northeastern United States, there has been a general buildup of ground level sulfates stretching many hundreds of miles *(29)*. This includes rural areas which have appreciable suspended particulate sulfate concentrations despite relatively negligible sulfur dioxide levels. In view of the possible toxicity of suspended sulfates, it should be noted that emission control measures designed to disperse sulfur dioxide from point sources, e.g., tall stacks, will not have a major effect on area-wide suspended sulfate levels despite producing a decrease in local ambient sulfur dioxide concentrations. Also of note is the finding that the ratio of sulfur dioxide to suspended sulfate concentrations in eastern cities differs from that in western cities *(30)*. Data from the last decade reveals the sulfur dioxide/sulfate ratio in eastern urban areas to be 4.9 (SO_2, 66 $\mu g/m^3$; SO_4, 13.5 $\mu g/m^3$) and in western urban areas to be 3.4 (SO_2 22 $\mu g/m^3$; SO_4, 6.4 $\mu g/m^3$).

The analytical techniques for the measurement of ambient concentrations of sulfur dioxide, suspended sulfates, and sulfuric acid are not comparable in terms of reliability or accuracy *(30, 31)*. Much information is available concerning ambient sulfur dioxide levels and the assay system is relatively well standardized and believed to be reasonably accurate. Less information about ambient suspended sulfate levels is available, and the assay systems in use have a number of difficulties. Most notable is the possibility that a portion of the sulfates detected on particle traps result from the reaction of sulfur dioxide with the trapping material and do not

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Table 4. Estimated sulfur dioxide oxidation rates in the lower atmosphere: tabulation of selected studies

Experimental conditions	Presumed atmospheric conditions	Extrapolated SO_2 consumption rate	Reference
Sunlight; High SO_2 concentrations; no other impurities present	SO_2; sunlight; clean air	0.5%/hr	Hall, *(22)*, cited by Urone and Schroeder *(23)*
Sunlamp in smog chamber; high SO_2 concentrations in pure air	SO_2; sunlight; clean air (reaction unaffected by humidity)	0.1–0.2%/hr	Gerhard and Johnstone *(6)*
Sunlight; 200–2000 $\mu g/m^3$ SO_2; trace impurities	Assuming 300 $\mu g/m^3$ SO_2; bright sunlight for 10 hr would produce 30 $\mu g/m^3$ of sulfate	0.65%/hr (high rate may be due to trace impurities)	Cox and Penkett *(24)*
Smog chamber; light; SO_2, NO_x, olefins	SO_2, 260 $\mu g/m^3$; ozone, 100 $\mu g/m^3$ olefin, 33 $\mu g/m^3$, bright sunlight	3%/hr for pentene; 0.4%/hr for propene	Cox and Penkett *(8)*
Photochemical reactants SO_2 in ppm concentrations	Sunlight; SO_2, 260 $\mu g/m^3$; ozone, 200 $\mu g/m^3$; olefin, 33 $\mu g/m^3$; 40% RH	3%/hr	Cox and Penkett *(9)*
UV-irradiated gas mixtures; NO_x, hydrocarbons, SO_2; high levels	Noon sun	1–3%/hr	Urone et al. *(12)*
Catalyst droplet exposed to high concentrations of SO_2 in humid air	Natural fog containing 1 μ crystals of $MnSO_4$ in droplets; 2600 $\mu g/m^3$ SO_2	1%/min	Johnstone and Coughanowr *(16)*
Metallic aerosol particles on Teflon beads in flow reactor; SO_2; water vapor	Natural fog (0.2 g H_2O/m^3) in industrial area; SO_2, 260 $\mu g/m^3$; $MnSO_4$, 50 $\mu g/m^3$	2%/hr	Cheng et al. *(13)*
Artificial fog in smog chamber; very high levels; SO_2 and metal sulfates	(Levels in smog chamber) 0.6 mg/m³ SO_2; 2 mg/m³ Mn SO_4,	0.01%/min at 77% RH 2.1%/min at 95% RH	Johnstone and Moll *(17)*
NH_4SO_4 formation in water droplets exposed to NH_3 and SO_2	100 $\mu g/m^3$ SO_2; 10 $\mu g/m^3$ NH_3; cloud droplet radius of 10 μ	2.5%/min in droplets	Van Den Heuvel and Mason *(21)*
Atmospheric study of polluted areas in Japan	—	11.7%/min	Shirai et al. *(25)*
Atmospheric study of Canadian smelting area	150–4200 $\mu g/m^3$ SO_2	0.035%/min	Katz *(26)*
Study of SO_2 oxidation in plume of coal-burning power plant	Found moisture level in plume important; SO_2 6 g/m³	0.1%/min at 70% RH 0.5%/min at 100% RH	Gartrell et al. *(27)*
Atmospheric study of Rouen (industrial city) in winter	68–242 $\mu g/m^3$ SO_2	6–25%/hr	Benarie et al. *(28)*

represent atmospheric sulfates. Another problem, perhaps related is the report that the concentration of sulfates in air depends upon the sampling volume. Much work needs to be done to solve these problems and to analyze critically and standardize the various sulfate measurements. Sampling and analysis of atmospheric sulfuric acid can most optimistically be described as in the development stage and further effort is required. Establishment of techniques to characterize the chemical composition of atmospheric sulfates is an essential step toward the understanding of health effects. It should be noted that as much as 80% of particulate sulfates collected in urban areas are in a size range small enough to be inhaled into the alveolus of the lung *(32, 33)*. In addition, further information is required concerning the relationship of ambient levels of sulfur dioxide to ambient levels of suspended sulfates. Available information suggests that this is not a simple linear function *(29)*.

In summary, evaluation of the atmospheric chemistry of sulfur oxides produces the following conclusions: (1) the rate of oxidation of sulfur dioxide to sulfuric acid and its conversion to suspended sulfates is greatly accelerated in polluted air; (2) the atmospheric chemistry of these reactions is highly complex and incompletely understood, and present information is mainly qualitative rather than quantitative; (3) in order to understand fully the relationship of ambient sulfur oxide levels to health effects, much more work is required to identify and characterize the various forms of sulfate present in the atmosphere, the processes by which they are produced, and their relationship to point or area sources of sulfur dioxide.

Background Review: Toxicology

The demonstration of a cause-and-effect relationship between exposure to sulfur oxides and adverse health consequences is based in part on experiments in which animals and human subjects are exposed to controlled atmospheres in the laboratory. Such studies permit the assessment of physiological changes caused by exposures of known duration to pollutants of known concentration. The controlled atmospheres used in laboratory experiments do not simulate urban air pollution accurately, and the detection of physiological responses does not necessarily indicate an adverse health effect. Nevertheless, studies in exposure chambers give clues to the kinds of effect to be expected from exposure to atmospheres containing the pollutants which have been studied in the laboratory.

SO_2 in Particle Free Air

Animal Studies: SO_2 is a respiratory irritant with high solubility in the aqueous lining membranes of the respiratory passages. Because of its high solubility, SO_2 is largely absorbed in the nose and upper respiratory passages and very little reaches the lungs. To produce death or pathological changes in the lungs of experimental animals, very high concentrations are needed. SO_2 inhalation produces bronchial narrowing as indicated by increased airflow resistance. This effect occurs in a matter of minutes and is readily reversible, suggesting that it results from an increase in bronchial smooth muscle tone *(35)*. The effect has been observed in guinea pigs, dogs, and cats as well as in human subjects. Exposure of guinea pigs to SO_2 levels up to 5.72 ppm (17,000 $\mu g/m^3$) for 12 months produced no identifiable effects apart from slight changes in the liver *(36)*. Monkeys exposed continuously for 78 weeks to SO_2 levels of 0.14–1.28 ppm (400–3800 $\mu g/m^3$) showed no significant pathological changes *(37)*. After exposure of rats to 1 ppm SO_2 (3,000 $\mu g/m^3$) for 170 hr, a significant depression of lung clearance of inert particles was demonstrated *(38)*. The effect of SO_2 was studied in Syrian hamsters who had been made emphysematous by exposure to an aerosol of 3% papain. The animals were exposed to high concentrations of SO_2 (650 ppm; 1,950,000 $\mu g/m^3$) for 4 hr per day, 5 days per week, for a total of 19–74 exposures. Only mild bronchitis and minor changes in the mechanical properties of the lungs were observed *(39)*. While conceptually attractive, this study is difficult to interpret because of the exceptional tolerance of the Syrian hamster to SO_2.

Human Studies: Although there is considerable variation in response in different people and in the same person at different times, most people show changes in respiratory flow resistance at SO_2 concentrations of 5 ppm (15,000 $\mu g/m^3$) and above. Especially sensitive people react to concentrations in the 1–2 ppm range (3000–6000 $\mu g/m^3$) *(35, 40–42)*. After 120 hr of exposure to 3 ppm (9000 $\mu g/m^3$) SO_2, increased small airway resistance and significant but minimal decrease in the dynamic compliance of the lung was noted in normal human subjects. The effect disappeared within 48 hr after cessation of exposure *(43)*. Four week-long exposures of subjects with demonstrable peripheral airway disease to SO_2 levels of 0.0, 0.3, 1.0, and 3.0 ppm (0, 900, 3000, and 9000 $\mu g/m^3$) produced no pattern relating to SO_2 dose *(44)*. The study was difficult to carry out, and the data showed wide variance.

In recent studies of normal human subjects, nasal mucus flow was measured by external detection of the movement of a very small radioactive particle placed on the mucosal surface inside the nose *(42)*. Mucus flow about half way from the tip of the nose to the nasopharynx decreased on the average to 80% of control values after 1–3 hr exposure to 1 ppm (3,000 $\mu g/m^3$) SO_2 in particle free air and decreased further to 54% of the control value after 4–6 hr exposure. Gas samples taken from the nasopharynx after passage through the nose contained less than 1% of the SO_2 which entered the nose, indicating that more than 99% had been absorbed in the nose. This confirmed earlier studies in animals and in healthy people. Mucus flow was slowest in the anterior part of the nose where the concentration of SO_2 was the highest, and was fastest in the posterior part of the nose where little SO_2 remained in the air. On forced expiration through the mouth, the air flow rate was reduced to an increasing degree with increasing concentrations of inspired SO_2 and with increased duration of exposure. In view of the very low concentrations of SO_2 reaching the bronchi, the reduced maximum expiratory air flow is thought to have resulted primarily from a nasobronchial reflex causing bronchoconstriction.

The absorption of SO_2 by the nose minimizes the exposure of the lower airways and lungs to SO_2, but interferes with mucus flow in the nose. This impairment of mucociliary clearance would be expected to reduce the capability of the respiratory tract for dealing with airborne particles, whether infectious, toxic, or inert, but direct evidence to this effect in humans is not yet available. When the nose is by-passed by breathing through the mouth, the trachea and bronchi are exposed to much higher concentrations of SO_2 than with nose breathing and adverse effects are greater.

SO_2 and Particulate Sulfur, Including Sulfuric Acid and Sulfate Salts

Mixtures of SO_2 and aerosols often have a greater irritant effect than would be expected from the two components acting independently *(35, 40, 41, 45)*. This more than additive effect, called synergism, is due to the transformation of SO_2, into a variety of products, including sulfuric acid and sulfate salts, which are more highly irritant than SO_2 itself.

Aerosols of soluble salts form droplets in humid air, and SO_2 dissolves in the droplets. This can occur in the atmosphere when the relative humidity is high or in the respiratory passages where the air rapidly becomes saturated with water vapor. The tiny droplets carry the SO_2 more deeply into the respiratory airways than it would otherwise go and also provide an aqueous medium in which chemical transformations can take place. Aerosols in the submicron size range penetrate more deeply and potentiate the irritant effect of SO_2 to a greater extent than larger particles. The irritant effect of a given droplet is increased by transformation of dissolved SO_2 into more highly irritant substances such as sulfuric acid and metallic sulfates.

Animal Studies: The synergism between SO_2 and particulates has been demonstrated by studies using mortality and lung pathology as criteria as well as in studies using changes in airway resistance and in clearance of inert particles and viable bacteria from the lungs *(35, 40, 41, 45)*. The presence of particulates capable of oxidizing SO_2 to sulfuric acid caused a 3- to 4-fold potentiation of the irritant response in guinea pigs *(41)*. Soluble salts of ferrous iron, manganese and vanadium were shown to pro-

duce this potentiation even at SO_2 concentrations as low as 0.16 ppm (480 $\mu g/m^3$). This concentration is occasionally seen in urban atmospheres. The metallic salts which acted as catalysts in these experiments were used at concentrations of 0.8 to 1 mg/m^3, which is higher than has been reported in urban air. Insoluble aerosols, such as carbon, iron oxide fume, triphenyl phosphate, or fly ash did not cause a potentiation of the irritant action of SO_2.

Recent experiments using guinea pigs have demonstrated that the synergism between SO_2 and aerosols of common salt, sodium chloride, are critically dependent on relative humidity *(46)*. At relative humidities above 70% the salt particles become droplets in which chemical reactions with SO_2 can occur before the aerosol is inhaled. Under these conditions synergism occurs as indicated by increase in airway resistance. Below 70% relative humidity the salt particles remain in the air as nonreactive crystals, and no synergistic effect upon airway resistance is seen. Since the humidity of air in the respiratory passages is always high, one can infer that the formation of droplets in the outside air, before entry into the airways, is of critical importance in relation to irritant effects.

Experiments in which animals were exposed to SO_2 alone or in combination with various insoluble dusts did not demonstrate increased susceptibility to bacterial infection *(47)*.

Mutagenic changes in viruses and bacteria have been attributed to the bisulfite ion which is one of the reaction products of SO_2 in water *(48–50)*.

Human Studies: Studies in which people have been exposed to combinations of SO_2 and sodium chloride aerosol have not consistently shown the synergistic effect seen in guinea pigs *(35, 41)*. Human exposures to mixtures of SO_2 and metallic aerosols which produce irritant sulfates have not been reported, and there are no human exposure data concerning combined effects of sulfur oxides and other commonly occurring pollutants such as nitrogen oxides, ozone, or hydrocarbons.

Summary

SO_2 and products into which it may be converted in the air are irritating to the lining membranes of the respiratory tract.

The irritant effect causes reflex bronchoconstriction, slowing of mucus flow, depression of clearance of inert particles from the lung, and, in regions of high concentration, narrowing of airways from inflammatory swelling of membranes.

Synergism between SO_2 and soluble aerosols has been demonstrated in animals. The necessary experiments have not yet been performed under controlled conditions using human subjects.

Increased susceptibility to infection has been looked for, but not found, in animal experiments, and has not been looked for in people under controlled conditions.

Bisulfite, one of the reaction products of SO_2 in droplets, has been shown to have mutagenic effects on viruses and bacteria. The significance of this finding to human health, if any, cannot yet be evaluated.

The physiological responses found under controlled conditions give useful insights into mechanisms of action, but cannot be translated directly into adverse effects of exposures to contaminated urban air.

Background Review: Epidemiology

Acute Episodes

The acute episodes of high pollution which have occurred in the Meuse Valley, Belgium, Donora, London, New York City, Osaka and elsewhere *(51–56)* provide the clearest evidence of an effect of air pollution on health. The increased mortality and morbidity which occurred in these episodes of pollution probably affected predominantly those who already were suffering from some chronic illness, particularly of the heart or lungs. These excess deaths occurred in age groups above 45 years in both London *(57)* and New York *(58)*; in addition, the individuals who were affected at Donora *(59)* were primarily those who had preexisting chronic disease. Gore and Shaddick *(60)* concluded from their analysis of episodes during the winters of 1954–1955 and 1955–1956 that a critical level of four times the customary winter average of air pollution in London would result in excess deaths. Subsequently, Burgess and Shaddick *(61)* suggested

that this would happen when smoke concentrations rose above $\mu g/m^3$ 2000 and SO_2 above 0.4 ppm (1144 $\mu g/m^3$).

Variation in Mortality, Morbidity, and Lung Function Over Time

Since 1958 in London, daily measurements of smoke and SO_2 have been related to daily deaths and illnesses *(62)*. Mortality and morbidity for all causes and for certain respiratory diseases were fairly highly correlated with both smoke and SO_2 levels until 1962; since 1962–1963, however, there has been little evidence of any effect of pollution on mortality or morbidity. It seems reasonable to attribute this change to the great reduction in smoke pollution which has been achieved in London during the last 15 years. During this time, smoke has declined from an average annual level of about 300 $\mu g/m^3$ to less than 50 $\mu g/m^3$ and SO_2 from a slightly higher concentration to about 200 $\mu g/m^3$. Lawther, reviewing these data for the period November 1958 to February 1959 concluded that increased mortality would result when daily smoke rose above 750 $\mu g/m^3$ and SO_2 above 0.25 ppm (710 $\mu g/m^3$).

Fletcher and his colleagues *(63)* made regular observations on 1000 men aged 30–59 living in North London from 1961 to 1966. The incidence of respiratory illnesses was found to be related to both smoke and SO_2 levels. Illness attack rates increased when weekly smoke concentrations exceeded 400 $\mu g/m^3$ and SO_2 exceeded 0.16 ppm (458 $\mu g/m^3$). An increase in symptoms and decrease in ventilatory lung function appeared to be associated with daily rises in smoke concentrations above 300 $\mu g/m^3$ and SO_2 concentrations above 0.21 ppm (600 $\mu g/m^3$). During the period of observation, there was a decline in the volume of morning sputum produced by the men under observation. This could have been due to the concurrent reduction in air pollution but it might also have been due to a reduction in the tar content of cigarettes, which also occurred at the same time.

In an attempt to study a more susceptible group of people, Lawther and his colleagues *(64–69)* have been making observations on bronchitic patients. Each patient keeps a daily record of changes in his health in a pocket diary, and records whether his chest is better, worse, or the same as usual. A close correlation between the concentration of smoke and SO_2 and the clinical condition of the patients during the winter months was noted. In the earlier years (1959–1960), the correlations were higher than 5 yr later (1964–1965), when the concentration of smoke in London had been considerably reduced. The patients appeared to be most sensitive to changes in pollution early in the winter. The minimum pollution level which leads to a significant response was about 500 $\mu g/m^3$ SO_2 with about 250 $\mu g/m^3$ smoke. These authors considered that the effects they observed were more likely to be due to brief exposures to the maximum concentrations occurring during the day than to the 24-hour daily levels. Moreover, they noted that correlations between health status and pollutant levels were still demonstrable in 1967–1968 when the annual concentration of smoke was 68 $\mu g/m^3$ and of SO_2 204 $\mu g/m^3$.

Studies of bronchitic patients were carried out in Chicago by Burrows et al. *(70)*. The severity of symptoms was found to vary with temperature and SO_2 level. When season and daily temperature were held constant, however, only hydrocarbon levels showed an independent correlation with symptoms. The authors concluded that air contaminants did not appear to play a major role in the daily variation in the patients' symptoms. However, Carnow et al. *(71)* who also studied patients in Chicago, found that illness rates increased with increasing exposure to SO_2. The critical level at which this increase occurred appeared to be about 0.25–0.30 ppm SO_2 (710–858 $\mu g/m^3$). Particulates were not included in this analysis. They were probably high since in 1966–1967, the time the study was carried out, the average annual concentration of particulates in Chicago was 148 $\mu g/m^3$.

Geographical Comparisons

One way in which the effects of pollution may be studied is to compare people who live in areas which differ in air pollution. Comparisons may be international, national, or local. They may be of persons living in urban and rural areas, in cities which differ in their pollution, or in different areas of a single large city.

International Differences

The large differences in bronchitis mortality among different countries has sometimes been

attributed to differences in pollution among them. But it has become increasingly clear that diagnostic practices differ in different countries, and that variations in death certification account for much of the variation. However, when these are allowed for, there are still differences in mortality and morbidity between different countries. Some of these could be due to differences in air pollution. Some of the difficulties inherent in carrying out international comparisons are indicated by the studies conducted by Ferris and Anderson *(72, 73)*. The authors compared respiratory disease and lung function in representative samples of the inhabitants of two towns which differed in their degree of air pollution. In 1961 they studied a 1:10 sample of adults living in Berlin, New Hampshire. Two years later, they carried out a comparable study of a 1:7 sample of the inhabitants aged 25–74 of Chilliwack, British Columbia. In each survey, methods were comparable and the observers the same. One major cause of differences between surveys was therefore largely eliminated.

Information about respiratory symptoms and smoking habits was obtained by using a prototype of the British Medical Research Council's respiratory symptoms questionnaire. The forced expiratory volume (FEV) and peak expiratory flow rates (PEFR) were used to assess ventilatory lung function. On the basis of the age/specific prevalence of symptoms in both surveys, expected rates for non-smokers were calculated. From the multiple regression equations on age and height for the FEV and PEFR for Berlin, expected lung function values were calculated for Chilliwack. There was little difference in respiratory disease prevalence of male non-smokers from that expected, but in women the prevalence was slightly below that expected. Lung function values were also consistently slightly higher than expected in both men and women in Chilliwack for all smoking categories. These differences are in the direction one would expect if pollution were exerting an effect. But, as the authors point out, they could still be due to ethnic differences between the two populations.

A further international comparison was made between the results from the general practitioners survey in Great Britain and that in Berlin, New Hampshire *(74, 75)*. In both instances the same questionnaire was used. In the British survey a panel of physicians was used whereas two other physicians surveyed the Berlin, New Hampshire population. No cross testing of the two groups of observers was done; but one of the observers in Berlin has worked with British workers using similar questionnaires and there have not been marked differences between the observers. A comparison of the results shows that Berlin, New Hampshire, has lower levels of particulates and SO_2 than the concentrations of large cities of Britain. The subjects were then categorized as simple chronic bronchitis (phlegm production for three months out of the year for the past 2–3 yr or more) or a complex chronic bronchitis (simple chronic bronchitis, plus bouts of cough and phlegm lasting for three weeks each winter and for more than two winters), and shortness of breath (such that the subject could not keep up with persons of his own age on the level). Only those 45–64 years of age were compared. When the data were standardized for cigarette smoking, no relationship was seen between the simple syndrome and air pollution. The complex syndrome, on the other hand, did show an increase across the levels of pollution which was approximately a 2 to 3-fold rise. A comparison of the tests of pulmonary function cannot be made with certainty as only peak flows were measured in Britain and there was no cross calibration of the meters. In general, values in the United Kingdom were lower for the same age, sex, and smoking category.

In another study a similar comparison was made between Britain and the United States and a comparable occupational group *(76)*. This study showed that the pulmonary function of the men in the United States was better than that in the United Kingdom. Differences in height in the two populations could not account for all of the difference. No statement was made as to the temperature corrections. If these results were expressed at ATPS, then the temperature differences between the two countries might account for the residual difference. The authors, however, attributed the difference to the different levels of pollution in the two countries.

Urban/Rural Gradients of Respiratory Disease Mortality and Morbidity

A striking feature of the mortality statistics of certain countries is a pronounced gradient between urban and rural areas in death rates for chronic respiratory disease. This trend is pronounced in the United Kingdom for both men and women. There is a similar, though much less impressive, trend for men, but none for women in the United States *(77)*. These observations have stimulated a great deal of research *(78–81)*. The earliest studies used available data *(82–86)*. Mortality rates in different areas were related to levels of air pollution where these were available. Mortality from bronchitis was found to be correlated with indices of pollution, social circumstances, and density of population. In many of these studies, however, cigarette smoking habits were not adequately controlled for.

Comparisons of Uniform Occupational Groups

To get around the difficulty that differences in exposure to air pollution tend to be confounded with differences in social class, Fairbairn and Reid *(87)* studied postmen, a uniform occupation group, who receive the same pay wherever they work and, once established, tend to remain in the same area. They found that premature retirement and death from bronchitis and pneumonia were related to thick and presumably polluted fog, and were independent of domestic overcrowding or population density. Somewhat similar observations were made in British transport workers *(88)*.

In the United States, surveys of Bell Telephone employees were carried out by Holland et al. *(89)* and by Deane et al. *(90)*. The results have been compared with studies carried out in a comparable manner in London and smaller towns in England. Differences in symptom prevalence, morning sputum volume, and lung function were observed, which were in a direction which would have been expected if pollution had been playing a role. A recent study of telephone workers in Washington, D. C., Baltimore, Manhatten, and Westchester County, N.Y., failed to show any significant association between pollution at home and at work and respiratory symptoms and level of ventilatory lung function *(91)*.

Comparisons between Towns

Comparisons have sometimes been made between towns which differ in air pollution. Dohan and Taylor *(92)* and Dohan *(93)* related claims for insurance benefits in female employees of the Radio Corporation of America to levels of pollution in five cities. They found a high correlation between respiratory illnesses of seven days' duration and over and average levels of suspended particulate sulfates for the years 1955–1957. Age distribution, conditions of work, and social and climatic factors did not appear to account for the five fold variation in the incidence of these illnesses between the cities.

A comparison of respiratory disease and lung function in two towns in Pennsylvania with contrasting levels of air pollution was carried out by the United States Public Health Service *(94)*. Average dust fall in Seward, the more polluted town, was 3.2 times and SO_2 was 6.2 times that of New Florence. Age- and height-adjusted mean values of most lung function tests were remarkably similar for both sexes in each town. The only exception was that the average airways resistance and airways resistance times volume were higher in Seward. It was not possible to conclude from this study that the difference in pollution caused the difference in airway resistance because there were other differences between the two towns (for example, the proportion of miners in each) which could have been responsible, and cigarette smoking was not controlled for.

Differences within a Large City

Differences in mortality and morbidity often occur in different areas of a single large city. It is sometimes possible to correlate these with differences in air pollution. Such studies have been carried out in Buffalo, New York *(95, 96)*. Pollution in Buffalo was monitored from 1961–1963, and levels of particulates and sulfation were related to mortality for 1959–1961. Total mortality in men and women aged 50 years and over and respiratory disease mortality in men

aged 50–69 were both significantly correlated with suspended particulate concentrations. There was no significant relationship between mortality and sulfation in this study, but the levels of sulfation recorded were low.

One of the most detailed studies of air pollution was conducted by the United States Public Health Service in Nashville, Tennessee *(97–99)*. Pollution was monitored by a network of 123 stations. Mortality from 1949 to 1960 was correlated with pollution levels. Age/specific death rates for respiratory disease at ages 25–74 were directly related to SO_2 levels and cardiovascular mortality to soiling. Various indices of morbidity, such as the frequency of asthma attacks, were also related to pollutant levels. Unfortunately, in neither the Buffalo nor Nashville studies was attention directed to smoking habits or occupation.

Studies of Children

A number of studies has been carried out on children, who are particularly suitable because they tend not to smoke cigarettes and for the most part do not engage in dusty jobs. They may also be exceptionally sensitive to the effects of pollution.

In Japan, Toyama *(100)* and Watanabe *(56)* found that school children living in Kawasaki and Osaka, two polluted cities, had lower peak flow rates than children living in less polluted areas. One of the most interesting studies of children was carried out in Britain by Douglas and Waller *(101)*. In 1946, a study of health and development was initiated. All children born in a one-week period in March were followed to school-leaving age in 1961. Subsequently, the illness experience of the children was related to the areas in which they had lived, and so to the probable levels of pollution experienced through life. The results showed that lower respiratory infections were consistently related to pollution but that upper respiratory infections were not. Both the frequency and severity of such infections increased with the amount of pollution. The lowest levels of smoke and SO_2 were 70 and 90 $\mu g/m^3$, respectively. Higher illness rates were added in all higher pollution classes.

Lunn et al. *(102)* studied the prevalence of respiratory illnesses in school children aged 5 years and 10 to 11 years living in four areas of Sheffield with differing air pollution. They found that both upper and lower respiratory infections increased with increasing pollution. The prevalence of symptoms was higher at annual means of smoke and SO_2 of about 200 $\mu g/m^3$ compared with about 100 $\mu g/m^3$. FEV and forced volume capacity (FVC) were lower in the most polluted area. A 4-yr follow-up *(103)* showed that most of the differences between the groups had disappeared with the reduction of smoke which had been achieved in Sheffield.

More recently, Holland et al. *(104)* studied some 10,000 school children in four areas of Kent. Peak expiratory flow was found to be related to area of residence, social class, family size, and a past history of pneumonia, bronchitis, or asthma. These four factors appeared to act independently and the effects were additive. The findings suggested that environment early in life can produce adverse changes which may persist and contribute to the development of chronic respiratory disease.

Ferris et al. *(105)* did a follow-up study in 1967 in the Berlin, New Hampshire population that had been studied in 1961. The levels of both sulfation rate and total suspended particulates had fallen by about 30–40%. After age standardizing within the various cigarette smoking categories, men and women tended to have lower frequencies of respiratory symptoms and less of a fall in pulmonary function than would have been expected by age. Levels of air pollution were 731 (±241) μg SO_2/100 cm^2/day in 1961 and 469 (±111) μg SO_2/100 cm^2/day in 1967; total suspended particulates were 180 ± 71 $\mu g/m^3$ in 1961 and 132 ± 83 $\mu g/m^3$ in 1967. Changes in smoking habits or use of filter-tipped cigarettes could not explain this difference. These results were interpreted as being confirmatory of those seen in the Berlin-Chilliwack comparison.

More recently, Cohen et al. *(106)* using a diary technique, looked at the effects of climate and air pollution on asthmatics. The sample was small. They found that temperature had more effect than air pollution and that all pollutants were associated with asthmatic attacks. There also seemed to be an interaction between temperature and pollution levels such that the effect

of the pollutants was greater at temperatures above 50°F than at temperatures below 30°F when the asthma attack rate was greatest.

A number of other studies have looked at these aspects and have concluded that there may well be such an interaction and that the effects of climate should be taken into account.

Lambert and Reid *(107)* carried out a postal survey of respiratory symptoms in a representative sample of men and women living in England, Wales, and Scotland. Of 18,379 men and women believed to be aged 35 or over in the households sampled, questionnaires were returned from 12,236. Of these, 2261 were outside the required age range of 35–69, 1155 refused, and 3614 did not reply. The 9975 questionnaires completed, thought to represent 74% of those aged 35–69 and able to respond, were analyzed. An increasing prevalence of persistent cough and phlegm and of chronic bronchitis (persistent cough and phlegm, breathlessness on walking, and a period of increased cough and phlegm lasting 3 weeks or more in the past 3 yr) with increasing age and with increasing cigarette consumption was confirmed. There was an excess in male nonsmokers as well as in smokers. Urban/rural gradients were not explained by smoking differences alone. The prevalence of symptoms increased with increasing air pollution independently of cigarette consumption. Local pollution appeared to have little effect on nonsmokers, but in smokers, high levels of pollution were associated with more frequent respiratory symptoms. Prevalence of symptoms increased progressively from the lowest (less than 100 $\mu g/m^3$ smoke and SO_2 on the average per year) to the highest (≥ 200 $\mu g/m^3$). This study, then, indicates that pollution had a clear effect on respiratory symptoms after allowing for age and cigarette smoking. There was also an interaction between smoking and pollution.

Recent Studies

During the past few years, as part of its Community Health and Environmental Surveillance System (CHESS), the Environmental Protection Agency has conducted a number of studies of the effects of air pollution on respiratory disease. Several of these have recently been published *(108–110)*. Levels of SO_2 and particulates, including suspended sulfates and nitrates, have been related to acute respiratory illnesses and chronic respiratory symptoms occurring in members of familes living in areas which differ in respect to pollution in four general communities. The communities were the Salt Lake basin area, Utah, five Rocky Mountain areas in Idaho and Montana, New York City and Chicago. Families were recruited through elementary or nursery schools. In the Utah and Rocky Mountain area, monthly averages of SO_2, sulfates and suspended particulates were derived from emissions estimates and dispersion models. Measurements were available only for 1971. In New York, total suspended particulates were collected daily by high volume sampler and analyzed for nitrate, sulfate, and organic fraction. SO_2 was measured three times a week by the modified West Gaeke method. In Chicago, particulates were measured three times a week and SO_2 once a week at an air monitoring station within 1.5 mile of the family's home. Health and demographic information on illnesses and respiratory symptoms was collected by self-administered questionnaires supplemented by telephone interviews. The questionnaires were completed for the family members by the mother or guardian. In each community the prevalence of chronic bronchitis (persistent cough and sputum for 3 months of the year either alone or with breathlessness when walking at an ordinary pace on the level) and the occurrence of various upper and lower respiratory tract infections in high and low pollution areas were compared. Higher rates were found in the higher pollution areas. A major aim of the studies was to define levels of pollution which resulted in an effect on health. The validity of self-reporting to accomplish this end is seriously open to question. Reporting is likely to reflect attitudes to present and past pollution and only limited checks of parental diagnoses with physicians records were made. One curious feature of the combined results of these studies in relation to chronic respiratory disease is that while in each community after allowance was made for smoking, the prevalence of chronic bronchitis was higher in the high than in the low pollution area, there were no corresponding differences between the communities. Chronic bronchitis was in fact lower in fathers and mothers in New York City

than in Utah despite the fact that pollution was much higher in New York City.

In a series of studies carried out in Cincinnati, Chattanooga, and New York City *(108)*, the forced expiratory volume of elementary school children was related to pollution. The FEV was found to be consistently lower in children 5–13 yr old exposed to higher concentrations of particulates and SO_2. In Cincinnati, the performance of children in polluted neighborhoods improved during the seasons of low pollution but not to the level of their counterparts in the low exposure neighborhoods. The results are presented graphically and in insufficient detail for the bases for these conclusions to be checked. Nor is sufficient evidence presented that differences between neighborhoods was not due to differences in the performance of the lung function test. We are not told who performed the test in each area. If a number of observers were involved, no measurements of observer variation were made. All in all, it is not at all clear that the differences in lung function between neighborhoods which were shown in these studies can be attributed to differences in air pollution between them.

In a recent study of bronchitic patients in London, Emerson *(111)* made several spirometric measurements at weekly intervals over periods of 12 to 82 weeks. The changes observed were correlated with daily atmosphere and air pollution measurements. Significant correlations of $FEV_{1.0}$ with temperature in six patients, humidity in four and with barometric pressure in three were found. In only one was there a correlation with SO_2 levels and in none with smoke. The conclusion drawn was that at the concentrations of these pollutants now existing in London SO_2 and smoke have little effect on ventilatory lung function of patients with chronic airways disease. The concentrations during this study were: smoke, mean annual 41 and maximum daily 241 $\mu g/m^3$; SO_2, mean annual 187 and maximum daily 730 $\mu g/m^3$. This study might perhaps suggest that, provided smoke concentrations are low enough, somewhat higher levels of SO_2 than are now permitted by the primary standards might be permitted.

On the other hand, a recent study of mortality in the United States *(112)* from 1962 to 1966 showed that while the main predictors of mortality were: annual cycle, day of the week, Christmas holidays, influenza epidemics and days or spells of extreme temperatures, pollution as measured by coefficient of haze units (COHS) and SO_2 contributed to a small but significant extent. In New York City, mortality was 1.5% less than expected when SO_2 was under 30 $\mu g/m^3$ and 2% greater when it was above 500 $\mu g/m^3$. This in fact suggests that there might be no threshold and that the lower the concentration of SO_2, the lower will be the possibility of adverse health effects.

Dose/Response Relationships, Old Results

We can form some idea of the levels of smoke and SO_2 which may cause effects (Table 5) *(113)*. It is important to realize that these two pollutants may not be the most important, but instead only indices of others that are more important. In London, mortality has clearly resulted when 24 hr concentrations of smoke have risen to 1000–2000 $\mu g/m^3$ and to concentrations of SO_2 of 750 $\mu g/m^3$. These sorts of levels may occur with average annual concentrations of smoke of 300–400 $\mu g/m^3$ and of SO_2 of 250–300 $\mu g/m^3$. No one can doubt that these concentrations are far too high and should not be allowed.

In London, 24 hr values of about 500 $\mu g/m^3$ smoke and 400 $\mu g/m^3$ SO_2 have led to exacerbations among bronchitis patients. Now that the average concentrations of smoke and SO_2 in London are about 40 and 170 $\mu g/m^3$, respectively, it will be interesting to see if there is still any response among these susceptible patients to the highest levels which occur in the winter.

In the whole of Britain, correlations which appear to be linear can be shown for bronchitis sickness absence when winter smoke and SO_2 rise above 100–700 $\mu g/m^3$. Similarly respiratory symptom prevalence and respiratory infections in children rise with increasing pollution levels above 100 microg/cu.m. In New York City, 24-hr averages of 6 coefficient of haze units (COHS) and 2000 $\mu g/m^3$ have resulted in mortality and 3 COHS and 700 $\mu g/m^3$ in morbidity.

In Buffalo, there was a steady increase in respiratory mortality from the lowest to the

Table 5. Summary of dose–response relationships for effects of particles and SO_2 and health.

Averaging time for pollution measurements	Approximate levels of pollution: Place	Particles, $\mu g/m^3$	SO_2, $\mu g/m^3$	Effect
24 hr	London	2000	1144	Mortality
24 hr [a]	London	750	700	Mortality
24 hr	London	300	600	Deterioration of patients
Weekly mean	London	200	400	Prevalence or incidence of respiratory illnesses
24 hr	New York	6[b]	1500	Mortality
Winter mean	Britain	100–200	100–200	Incapacity for work from bronchitis
Annual	Britain	70	90	Lower respiratory infections in children
	Britain	100	100	Upper and lower respiratory infections in children
	Britain	100	100	Brochities prevalence
	Britain	100	100	Prevalence of symptoms
	Buffalo	100	300[c]	Respiratory mortality
	Berlin, N.H.	180	731[c]	Increased respiratory symptoms Decreased pulmonary function

[a] "Old" results, leading to original standards.

[b] In coefficient of base units (COHS).

[c] As $\mu g\ SO_3/100\ cm^2$/day.

highest pollutant levels. The lowest particulates levels were under 80 $\mu g/m^3$ and sulfation was less than under 0.30 mg SO_3/cm^2/day.

On the basis of these figures, average annual values of something under 100 $\mu g/m^3$ for particulates and SO_2 and something under 300 and 600 $\mu g/m^3$ for 24 hr would seem to be desirable. The primary standards reflected this. What conclusions can be drawn from more recent studies about their adequacy?

New Results

The CHESS studies have provided the largest body of data which might perhaps suggest that the primary standards may be too high and should be lowered. We believe that the methods used, the sampling, the internal inconsistency of the findings and other questions render the validity of the findings too uncertain to justify these conclusions. Nor do we think that these studies provide a sound basis for a standard for suspended sulfates. More research is needed on this topic. British experience might suggest that the major effort should be put on reducing particulates. We are in some difficulty, however, in trying to generalize from British experience since the type of pollution and methods of assessing it are different in Britain and in the United States.

With the implementation and enforcement of the primary Federal air pollution standards, we have reached a stage where pollution is unlikely to cause much adverse effect on health. Further reduction of the standard might protect a few sick people from being made worse by air pollution, but of this there is considerable doubt (Table 6). Such reduction would be disproportionately costly when related to the likely benefits which could be expected. Such cost should only be accepted on the basis of convincing evidence that standards are now too high. The only satisfactory evidence that would justify this conclusion would come from well designed experiments. It would be justifiable to select some comparable cities; monitor pollution and inhabitants carefully, employing objective tests wherever possible; reduce particulates and SO_2 in one city, particulates in another, possibly enforce particulates at standard but allow SO_2 to rise modestly in a third and maintain standards in a fourth (Figure 4). The costs and benefits of the various procedures might then be adequately measured. We doubt if the information we now need can be obtained in any other way.

Table 6
Expected Health Effects of Air Pollution On Selected Population.

Effect	Pollutant	
Excess mortality and hospital admissions (24 hr mean)	500	500
Worsening of patients with pulmonary disease (24 hr mean)	250	500–250
Respiratory symptoms (annual arithmetic mean)	100	100
Visibility and/or annoyance (annual geometric mean)	80	80
World Health Organization (WHO) data.		

Maintain* TSP Maintain SO_2	Maintain TSP Allow SO_2 to rise (say, to 100 $\mu g/m^3$)
Reduce TSP Maintain SO_2	Reduce TSP Reduce SO_2

FIGURE 4. Experimental design. Asterisk (*) refers to primary Federal standards.

Interim Report: Review of Health Effects of Sulfur Oxides in the Ambient Air

Preliminary Findings

Following review of the available data and presentations by experts from the United States and abroad, it seems that the current primary ambient air standards for sulfur oxides (SO_2) are likely to be reasonable and in the proper range. We are continuing our analysis of the data in this area and will present more specific conclusions in our final report.

Nature of the Scientific Problem

SO_2 is a gas whose concentration in the atmosphere is used as an index of the extent of air pollution. When studied alone, it acts as a relatively nontoxic gas. In the ambient air, it undergoes chemical reaction to much more toxic substances, namely suspended sulfate particles and sulfuric acid mist. Additional epidemiologic studies are needed to verify the health effects of these products. These studies will require the development of improved monitoring methods and the establishment of a complete data base for sulfates (particularly in the particulate fraction) in the air. SO_2 levels in the ambient air appear to be a reflection of air pollution levels since SO_2 is the major precursor of the more toxic sulfur reaction products.

Nature of Standards

A Primary Ambient Air Standard states the concentrations of a given substance which on the basis of the "best available scientific evidence" are likely to cause no adverse health effects to the general population in the United States. "Best available scientific evidence" is an important concept because it indicates that the standards will change as we gather more knowledge about health effects of individual pollutants. With scientific advances, this standard will approach a "no effects level" for each pollutant based on a natural law of chemical-biological interaction. As we approach this natural limit, our margin of scientific error decreases. The Clean Air Act requires that a safety factor be added to each air quality standard to approximate the scientific error and to insure that the American people are adequately protected from the health consequences of each agent. Thus, the Primary Standard is the scientist's best estimate of a natural law of chemical-biological interactions which defines the highest concentration of a pollutant that will cause no damage to health. It includes an estimate of scientific error in terms of a legal safety factor.

Policy Decisions and the Standard

In the long run we are convinced that this identification of the natural law relationship will establish concentrations of SO_2 and other pollutants which do not damage human health. SO_2

levels however must not be considered in a scientific vacuum. We are well aware that modern man lives in a society which exposes him to a surprising variety of interrelated risks. Once these laws are identified, the difficult choices between interrelated risks can be made on an objective, scientific basis. In extreme situations, one standard or another might be appropriately and knowingly exceeded so as to ameliorate a related situation and thus cause the least possible harm to human health.

REFERENCES

1. Buechley, R. W. Arch. Environ. Health **27:** 137 (1973).
2. Wadell, T. 1973.
3. Lave, L. 1973.
4. Grey, D. C., and Jensen, M. L. Bacteriogenic sulfur in air pollution. Science **177:** 1099 (1972).
5. Kellogg, W. W., et al: The sulfur cycle. Science **175:** 587 (1972).
6. Gerhard, E. R., and Johnston, H. F. Photochemical oxidation of sulfur dioxide in air. Ind. Eng. Chem. **47:** 972 (1955).
7. Cox, R. A., and Penkett, S. A. Photo-oxidation of atmospheric SO_2. Nature **229:** 487 (1971).
8. Cox, R. A., and Penkett, S. A. Oxidation of atmospheric SO_2 by products of the ozone–olefin reaction. Nature **230:** 321 (1971).
9. Cox, R. A., and Penkett, S. A. Aerosol formation from sulphur dioxide in the presence of ozone and olefinic hydrocarbons. J. Chem. Soc. **68:** 1735, 1972.
10. Prager, M. J., et al: Aerosol formation from gaseous air pollutants. Ind. Eng. Chem. **52:** 521 (1960).
11. Sidebottom, H. W., et al. Photo-oxidation of sulfur dioxide. Environ. Sci. Technol. **6:** 72 (1972).
12. Urone, P., et al. Static studies of sulfur dioxide reactions in air. Environ. Sci. Technol. **2:**611 (1968).
13. Cheng., R. T., Corn, and Frohliger. Contribution to the reaction kinetics of water soluble aerosols and SO_2 in the air at ppm concentrations. Atmos. Environ. **5:** 987 (1971).
14. Chun, K. C., and Quon, J. E. Capacity of ferric oxide particles to oxidize sulfur dioxide in air. Environ. Sci. Technol. **7:** 532 (1973).
15. Foster, P. M.: The oxidation of sulphur dioxide in power station plumes. Atmos. Environ. **3:** 157 (1969).
16. Johnstone, H. F., and Coughanowr, D. R. Absorption of sulfur dioxide from air: oxidation in drops containing dissolved catalysts. Ind. Eng. Chem. **50:**1169 (1958).
17. Johnstone, H. F., and Moll, A. J.: Formation of sulfuric acid in fogs. Ind. Eng. Chem. **52:** 861 (1960).
18. Junge, C. E., and Ryan, T. G. Study of the SO_2 oxidation in solution and its role in atmospheric chemistry. Quart. J. Roy. Meteor. Soc. **84:** 46 (1958).
19. McKay, H. A. C. The atmospheric oxidation of sulphur dioxide in water droplets in presence of ammonia. Atmos. Environ. **5:** 7 (1971).
20. Smith, B. M., et al. Interaction of airborne particles with gases. Environ. Sci. Technol. **3:** 558 (1969).
21. Van Den Heuvel, A. P., and Mason, B. J. The formation of ammonium sulphate in water droplets exposed to gaseous sulphur dioxide and ammonia. Quart. J. Roy. Meteor. Soc. **89:** 271 (1963).
22. Hall, T. C., Jr. Ph. D. thesis cited by Urone and Schroeder *(29)* and Cox and Penkett *(24)*.
23. Urone, P. and Schroeder, W. H. SO_2 in the atmosphere: A wealth of monitoring data but few reaction rate studies. Environ. Sci. Technol. **3:** 436 (1969).
24. Cox, R. A., and Penkett, S. A.: The photo-oxidation of sulphur dioxide in sunlight. Atmos. Environ. **4:** 425 (1970).
25. Shirai, J. et al. Cited by Urone and Schroeder *(23)*.
26. Katz, M. Photoelectric determination of atmospheric SO_2 employing dilute starch-iodine solutions. Anal. Chem. **22:** 1040 (1950).
27. Gartrell, F. E., et al. Atmospheric oxidation of SO_2 in coalburning power plant plumes, TVA. Am Ind. Hyg. Assoc. J. **24:** 113 (1963).
28. Benarie, M. Et al: Étude de la transformation de l'anhydride sulfureux en acide sulfurique en relation avec les données climatologiques, dans un ensembly urbain in a caractère industriel, Rouen. Atmos. Environ. **7:** 403 (1973).
29. Altshuller, A. P. Atmospheric sulfur dioxide and sulfate. Distribution of concentration at urban and nonurban sites in United States. Environ. Sci. Techol 7:709 (1973).
30. U. S. Environmental Protection Agency: Summary report on suspended sulfates and sulfuric acid aerosols. Draft presented Aug. 1973.
31. Forrest, J., and Newman, L.: Ambient air monitoring for sulfur compounds: A critical view. J. Air Poll. Control Assoc. **23:**761 (1973).
32. Ludwig, F. L., and Robinson, E. Size distribution of sulfur-containing compounds in urban aerosols. J. Colloid. Sci. **20:** 571 (1965).
33. Wagman, J., et al. Influence of some atmospheric variables on the concentration and particle size distribution of sulfate in urban air. Atmos. Environ. **1:**479 (1967).
34. Atkins, D. H. F., et al: Photochemical ozone and sulphuric acid aerosol formation in the atmosphere over southern England. Nature **235:**372 (1972).
35. Air Quality Criteria for Sulfur Oxides, NAPCA, Publication AP-50. U.S. Government Printing Office, Washington, D. C., 1970.
36. Alarie, Y., et al. Long-term continuous exposure of guinea pigs to sulfur dioxide. Arch. Environ. Health **21:** 769 (1970).
37. Alarie, Y., et al Long-term continuous exposure to sulfur dioxide and cynomolgus monkeys. Arch. Environ. Health **24:** 115 (1972).
38. Ferin, J., and Leach, L. J. The effect of SO_2 on lung clearance of TiO_2 particles in rats. Am. Indus. Hyg. Assoc. J. **34:** 260 (1973).

39. Goldring, I. P., et al. Pulmonary effects of sulfur dioxide exposure in the Syrian hamster. Arch Environ. Health **21:** 32 (1970).
40. Air Quality Criteria and Guides for Sweden in Regard to Sulfur Dioxide and Suspended Particulates. Nord. Hyg. Tidsk. (Vol. 54, Suppl. 5, Stockholm, 1973).
41. Amdur, M. O. Toxicologic appraisal of particulate matter, oxides of sulfur, and sulfuric acid. J. Air Pollution Control Assoc. **19:** 638 (1969).
42. Andersen, I., et al. Human response to controlled levels of sulphur dioxide. Arch. Environ. Health, **28:** 31 (1974).
43. Weir, F. W., and Bromberg, P. A. Further investigation of the effects of sulfur dioxide on human subjects. American Petroleum Institute Project No. CAWC S-15, June 1972.
44. Weir, F. W., and Bromberg, P. A. Effects of sulfur dioxide on human subjects exhibiting peripheral airway impairment. American Petroleum Institute Project No. CAWC S-15, September 1973.
45. Rylander, R., Ohrstrom, M., and Bergstrom, R. SO_2 and particles synergistic effects of guinea-pig lungs. In: Inhaled Particles III. S. H. Walton, Ed., Unwin Bros., London, 1971, pp. 535–541.
46. McJilton, C., Frank, N. R., and Charlson, R. The role of relative humidity in the synergistic effect of SO_2 aerosol mixture on the lung. Science, **182:** 503 (1973).
47. Battigelli, M. C., et al. Long-term effects of sulfur dioxide and graphite dust on rats. Arch. Environ. Health **18:** 602 (1969).
48. Hayatsu, H., and Miura, A. The mutagenic action of sodium bisulfite. Biochem. Biophys. Res. Commun. **39:** 156 (1970).
49. Mubai, F., Hamrylub, I., and Shapiro, R. The mutagenic specificity of sodium bisulfite. Biochem. Biophys. Res. Commun. **39:** 983 (1970).
50. Summers, G. A., and Drake, J. W. Bisulfite mutagenesis in bacteriophage T4. Genetics **68:** 603, 1971.
51. Firket, J.: The cause of the symptoms found in the Meuse Valley during the fog of December 1930. Bul. Roy. Acad. Med. **11:** 683 (1931).
52. Schrenk, H. H., et al. Air pollution in Donora, Pennsylvania. Epidemiology of the unusual smog episode of October 1948. Preliminary report. Pub. Health Bull. **306:** 1949.
53. Logan, W. P. D. Mortality in the London Fog Incident, 1952. Lancet **1:** 336 (1953).
54. Greenburg, L., et al. Air pollution and morbidity in New York City. JAMA **182:** 161 (1962).
55. Greenburg, L., et al. Report of an air pollution incident in New York City, November 1953. Pub. Health Repts. **77:** 7 (1962).
56. Watanabe, H. Air pollution and its health effects in Osaka. Paper presented at 58th Annual Meeting, Air Pollution Control Association, Toronto, Canada, June 20–24, 1965.
57. U. K. Ministry of Health Mortality and morbidity during the London fog of December 1952. Report on Public and Medical Subjects No. 95 H.M.S.O., London, 1954.
58. Greenburg, L., et al. Intermittent air pollution episodes in New York City, 1962. Publ. Health Repts. **78:** 1061 (1963).
59. Ciocco, A., and Thompson, D. J.: A follow-up of Donora ten years after: Methodology and findings. Amer. J. Pub. Health. **51:** 155 (1961).
60. Gore, A. T., and Shaddick, C. W.: Atmospheric pollution and mortality in the county of London. Brit. J. Prev. Soc. Med. **12:** 104 (1958).
61. Burgess, S. G., and Shaddick, C. W. Bronchitis and air pollution. Roy. Soc. Health. **1:** 10 (1959).
62. Martin, A. E.: Mortality and morbidity statistics and air pollution. Proc. Roy. Soc. Med. **57:** 969 (1964).
63. Fletcher, C. M., et al. A five-year prospective field study of early obstructive airway disease. Current Research in Chronic Respiratory Disease, Proceedings of the Eleventh Aspen Conference. U. S. Department of Health, Education, and Welfare, Public Health Service, 1968.
64. Waller, R. E., and Lawther, P. J. Further observations on London fog. Brit. Med. J. **2:** 1356 (1955).
65. Waller, R. E., and Lawther, P. J. Further observations on London fog. Brit. Med. J. **2:** 1473 (1957).
66. Lawther, P. J. Climate air pollution and chronic bronchitis. Proc. Roy. Soc. Med. **51:** 262 (1958).
67. Lawther, P. J. Compliance with the Clean Air Act: Medical aspects. J. Inst. Fuel, **35:** 341 (1963).
68. Lawther, P. J. Air pollution and chronic bronchitis. Med. Thorac. **24:** 44 (1967).
69. Lawther, P. J., Waller, R. E., and Henderson, M. Air pollution and exacerbations of bronchitis. Thorax. **24:** 525 (1970).
70. Burrows, B., Kellogg, A. L., and Buskey, J.: Relationship of symptoms of chronic bronchitis and emphysema to weather and air pollution. Arch. Environ. Health **16:** 406 (1968).
71. Carnow, B. W., et al. The Chicago air pollution study: SO_2 levels and acute illness in patients with chronic bronchial pulmonary disease. Arch. Environ. Health, **18:** 768 (1969).
72. Ferris, B. G., and Anderson, D. O. Epidemiological studies related to air pollution: A comparison of Berlin, New Hampshire, and Chilliwack, British Columbia. Proc. Roy. Soc. Med. **57:** 979 (1964).
73. Ferris, B. G., and Anderson, D. O.: The prevalence of chronic respiratory disease in a New Hampshire Town. Am. Rev. Resp. Dis. **86:** 165 (1962).
74. College of General Practitioners. Chronic bronchitis in Great Britain. A national survey carried out by the respiratory diseases study group of the College of General Practitioners. Brit. Med. J. **2:** 973 (1961).
75. Reid, D. D., et al. An Anglo-American comparison of the prevalence of bronchitis. Brit. Med. J. **2:** 1487 (1964).
76. Holland, W. W., et al. Respiratory disease in England and the United States. Studies of comparative prevalence. Arch. Environ. Health. **10:** 338 (1965).
77. Manos, N. U. S. Public Health Service Publ. No. 562, 1957.
78. Christensen, O. W., and Wood, C. H. Bronchitis mortality rates in England, Wales, and Denmark. Brit. Med. J. **1:** 620 (1958).

79. Mork, T. A comparative study of respiratory disease in England and Wales and Norway. Acta. Med. Scand. **172:** Supplement 384 (1962).
80. Olsen, H. C., and Gilson, J. C. Respiratory symptoms, bronchitis, and ventilatory capacity in man. An Anglo-Danish comparison with special reference to smoking habits. Brit. Med. J. **1:** 450 (1960).
81. Reid, D. D. Air pollution as a cause of chronic bronchitis. Roy Soc. Med. **57:** 965 (1964).
82. Pemberton, J., and Goldberg, C. Air pollution and bronchitis. Brit. Med. J. **2:** 567 (1954).
83. Daly, C. Air pollution and bronchitis. Brit. Med. J. **2:** 687 (1954).
84. Daly, C. Air pollution and causes of death. Brit. J. Prev. Soc. Med. **13:** 14 (1959).
85. Stocks, P. Cancer and bronchitis mortality in relation to atmospheric deposit and smoke. Brit. Med. J. *1:* 74 (1959).
86. Buck, S. F., and Brown, D. A. Mortality from lung cancer and bronchitis in relation to smoke and sulphur dioxide concentration, population density and social index. Tobacco Research Council Research Paper No. 7, Tobacco Research Council, London, 1964.
87. Fairbairn, A. S., and Reid, D. D. Air pollution and other local factors in respiratory disease. Brit. J. Prev. Soc. Med. **12:** 94 (1958).
88. Cornwall, C. J., and Raffle, R. A. B. Bronchitis —sickness absence in London transport. Brit. J. Ind. Med. **18:** 24 (1961).
89. Holland, W. W., and Stone, R. W. Respiratory disorders in U.S. east coast telephone men. Am. J. Epidemiol. **82:** 92 (1965).
90. Deane, M., Goldsmith, J. R., and Tuma, D. Respiratory conditions in outside workers. Report on outside plant telephone workers in San Francisco and Los Angeles. Arch. Environ. Health **10:** 323 (1965).
91. Comstock, G. W., et al. Respiratory findings and urban living. Arch. Environ. Health **27:** 143 150 (1973).
92. Dohan, F. C., and Taylor, E. W. Air pollution and respiratory disease, a preliminary report. Am. J. Med. Sci. **240:** 337 (1960).
93. Dohan, F. C. Air pollutants and incidence of respiratory disease. Arch. Environ. Health **3:** 387 (1961).
94. Prindle, R. A., Comparison of pulmonary function and other parameters in two communities with widely different air pollution levels. Am. J. Publ. Health **53:** 200 (1963).
95. Winkelstein, W. The relationship of air pollution and economic status to total mortality and selected respiratory system mortality in man. Arch. Environ. Health **14:** 162 (1967).
96. Winkelstein, W., et al. The relationship of air pollution and economic status to total mortality and selected respiratory system mortality in men. II. Oxides of sulfur. Arch. Env. Hlth. **16:** 401, 1968.
97. Zeidberg, L. D., Prindle, R. A., and Landau, E. The Nashville air pollution study. I. Sulfur dioxide and bronchial asthma. A preliminary report. Am. Resp. Dis., **84:** 489 (1961).
98. Zeidberg, L. D., Prindle, R. A., and Landau, E.: The Nashville air pollutoin study. III. Morbidity in relation to air pollution. Am. J. Publ. Health **54:** 85 (1964).
99. Zeidberg, L. D., et al. The Nashville air pollution study. V. Mortality from diseases of the respiratory system in relation to air pollution. Arch. Environ. Health **15:** 214 (1967).
100. Toyama, T.: Air pollution and its health effects in Japan. Arch. Environ. Health. **8:** 153 (1964).
101. Douglas, J. W. B., and Waller, R. E. Air Pollution and respiratory infection in children. Brit. J. Prev. Soc. Med. **20:** 1 (1966).
102. Lunn, J. E., Knowelden, J., and Handyside, A. J. Patterns of respiratory illness in Sheffield Infant School children. Brit. J. Prev. Soc. Med. **21:** 7 (1967).
103. Lunn, J. E., Knowelden, J., and Roe, J. W. Patterns of illness in Sheffield Junior School children. Brit. J. Prev. Soc. Med. **24:** 223, 1970.
104. Colley, J. R. T., and Holland, W. W. Social and environmental factors in respiratory disease. Arch. Health **14:** 157 (1967).
105. Ferris, B. G., et al. Chronic non-specific respiratory disease in Berlin, New Hampshire, 1961–1967, a follow-up study. Am. Rev. Resp. Dis. **107:** 110 (1973).
106. Cohen, A. A., et al. Asthma and air pollution from a coal fueled power plant. Am. J. Publ. Health **62:** 1181 (1972).
107. Lambert, P. M., and Reid, D. D. Smoking, air pollution and bronchitis in Britain. Lancet **1:** 853 (1970).
108. Shy, C. M., et al. Air pollution effects on ventilatory function of United States school children. Results of studies in Cincinnati, Chatanooga, and New York. Arch. Environ. Health **27:** 124 (1973).
109. French, J. G., et al. The effect of sulfur dioxide and suspended sulfates on acute respiratory disease. Arch. Environ. Health **27:** 129 (1973).
110. Chapman, R. S., et al. Chronic respiratory disease in military inductees and parents of school children. Arch. Environ. Health **27:** 138(1973).
111. Emerson, P. A., Air pollution, atmosphere conditions and chronic airways obstruction. J. Occup. Med. **15:** 635 (1973).
112. Buechley, R. W., et al SO$_2$ levels and perturbations in mortality. A study in the New York-New Jersey metropolis. Arch. Environ. Health **27:** 134 (1973).
113. Higgins, I. T. T., Sulfur oxides and particulates in Medical Aspects of Air Pollution, Continuing Engineering Education, Society of Automotive Engineers, Detroit, Jan. 14, 1974.

MODIFICATIONS OF REGULATIONS

Mr. FLOOD. On page 4 you say "The new evidence raises questions not only about the adequacy of regulations designed to protect asbestos workers but also about the hazards the general public may face from exposure to asbestos fibers." That is the end of the quotation.

What are you doing to modify the regulations in order to protect the workers and the general public?

Dr. RALL. We have no regulatory function.

The people who modify the regulation are in OSHA, Department of Labor or EPA.

Mr. FLOOD. Both the Institute of Occupational Safety and Health and Occupational Safety and Health Administration, they must get involved. I do not see how they can miss if regulations are to be changed. Hopefully they are all working together. Are they or are they not?

Dr. RALL. I think so. We work very closely with NIOSH. I am very pleased that Jack Finklea is the new Director.

Mr. FLOOD. How do you translate that?

Dr. RALL. National Institute of Occupational Safety and Health.

Mr. FLOOD. Thank you.

Dr. RALL. Dr. Finklea worked in North Carolina across the street from us for many years. We are delighted an old friend is in that Institute now.

DIETHYLSTILBESTROL (DES)

Mr. FLOOD. When do you think you will have all the facts in hand in order to resolve the controversy surrounding the business of diethylstilbestrol (DES)? Is that still widely used as an additive for fattening cattle?

Dr. RALL. It currently is being used to fatten cattle. The FDA's ban was overturned about this time last year on procedural matters and it has not yet been reinstated. Let me make it clear that the amount of exposure a man or woman would get from eating beef cattle that had been fattened with the aid of DES is very, very, much less than the sort of exposure women got when they were given DES as a therapeutic drug.

What we are concerned now about primarily is the group of children of mothers who 10 to 20 years ago were given this compound as a therapeutic agent. They got very high doses, whereas you probably would get no DES from eating beef, the muscle, the meat of a calf or young cattle fed DES. The only DES that appears is in the liver. So if you avoid eating calves liver fattened on DES, you will have no exposure at all.

Mr. OBEY. Would you yield?

What about fat, is there no effect there?

Dr. RALL. The DES is almost all in the liver. Generally it is in an altered form.

Mr. FLOOD. All right, suppose a lot of people want some calves liver. How do you know whether or not it has received this?

Dr. RALL. You don't right now. I presume FDA is in the process of redrafting their regulations. I suspect following the Delaney Amendment they will reinstate the ban on using DES.

ENVIRONMENTAL HEALTH SCIENCES CENTERS

Mr. FLOOD. Last year you told us you were going to add one more environmental health science center. Did you add the center?

Dr. RALL. We are in the process of adding it.

Mr. FLOOD. You never added it?

Dr. RALL. It is being negotiated right now.

Mr. FLOOD. We would like to know where it is going to be located and what will the area's responsibility be.

Dr. RALL. It will very likely be in the University of Rochester in New York. The Director will be Dr. Thomas Clarkson, who is literally the world's authority on mercury poisoning and heavy metal toxicity in general.

We think this will be a superb group that will give us considerably added expertise in the whole area of heavy metals, cadmium, mercury, lead, et cetera.

SHORT-TERM QUALITATIVE TESTS

Mr. FLOOD. In your opening statement you said that the Institute scientists have made significant advances in developing short-term qualitative tests for agents that cause genetic damage. What do you mean by short-term qualitative tests? How are they used?

Dr. RALL. These are tests which can be done in a small glass dish in the lab and take only a few days or a week. They use cells, either bacterial, yeast or cultured mammalian cells. The test compound is added and the technician or scientist looks for changes in the biochemistry of the cell culture. Certain of these changes indicate that mutational events have occurred. By this I mean there has been a change in the ability of the organism to transmit the information necessary to provide a daughter cell of the same type.

Mr. FLOOD. What kind of cell?

Dr. RALL. A daughter cell, an offspring.

We think this can potentially replace whole animal tests which takes months to years to perform, require large amounts of space to house the animals and require expensive and very rare pathologists to study the animals when the experiment is through.

AF–2

Mr. FLOOD. You mention in your statement that the compound AF–2 we were talking about was eliminated from food preservations used in Japan. Is the compound used in this country?

Dr. BALL. No. It has never been used in the United States.

NATURAL AND SYNTHETIC SUBSTANCES

Mr. FLOOD. On page 200 of the justifications you say, "Research on the isolation and toxicity of natural and synthetic substances in food is being supported."

Specifically what substances are you talking about there?

Dr. RALL. Everything from the naturally occurring molds, the aflatoxins are a classic example of this to such added substances as nitrites.

The aflatoxin is an old and serious one in the world when peanuts or corn or grain are stored in a humid place with warm temperature.

Various molds grow on those peanuts being stored. Most of these molds have no particular toxic effects, in fact, penicillin grew on this. But some of them are very highly toxic. They cause serious liver damage, cirrhosis, birth defects or carcinogenesis. This is a major problem in some of the areas in the underdeveloped countries and in the less developed parts of the United States.

So these toxic molds are a general class. The other general class is the food additives. We still have the problem of nitrites which are added to meat and similar products to prevent bacterial growth, particularly botulism. The nitrites can act in the stomach with other compounds to produce a highly carcinogenic nitrosamine compound. We are here faced with preventing the growth of the organism that causes botulism and the possibility that the nitrites react in the human stomach and make a cancer producing compound. That is a very difficult tradeoff to make.

PESTICIDES

Mr. FLOOD. On page 200 you state, "Some pesticides have been found to disrupt function and influence behavior and learning patterns."

Which pesticides are you talking about? Are these products still on the market?

Dr. RALL. Yes, they are. These are the organophosphate pesticides which inhibit cholinesterase. There is mounting evidence that repeated exposure may cause neurological effects, changes in the electroencephalograph, the brain wave pattern.

No effects that you can measure on man have been documented. There have been documented effects on experimental animals exposed to such compounds for long periods of time. We are actively investigating this. We think it is potentially a serious problem.

TRAVEL

Mr. FLOOD. Doctor, your travel budget averages about $1,400 a year for each permanent position. That's higher than the average for many of the programs.

Can you explain this?

Dr. RALL. Much of the "excess" travel that we must make compared to the other Institutes, I think is simply due to the fact that we are located 280 miles away from here.

Mr. FLOOD. Yes; that is the commuting business.

Dr. RALL. Yes, sir.

Mr. FLOOD. Would you provide the detail of how this request for travel was computed?

Dr. RALL. Yes, we shall.

[The information follows:]

To estimate the Institute's future travel costs, it was necessary that the Institute review its past travel history and compare it to future plans. We are essentially holding our travel at the same level as 1975 and 1974, in spite of greatly increased interagency liaison. Much of our travel is obligatory such as that associated with site visits for grant applications, research contracting, attendance at conferences and symposiums, and the travel of my staff and myself bewteen the Research Triangle and Washington, D.C. on official business.

OTHER SERVICES

Mr. FLOOD. You are requesting an increase of $303,000 for "Other services."

What are these other services and why is such an increase necessary when you are decreasing your research grants and contracts and up goes this "Other services."

Dr. RALL. Many of these "Other services," and I will tell you about them in a minute, are just the necessary part of doing business. For instance, we have to maintain the grounds of our Institute. We don't have NIH to take care of them for us. The cost of business is simply going up. We have to provide janitorial and linen service for our Institute. These we pay for out of "Other services." Repairs and alterations to our facilities come out of "Other services." For instance, we managed to obtain on government surplus a small calculator, a small computer, an IBM 1620. We had to alter, renovate two rooms to allow us to install this computer.

Mr. FLOOD. A small computer?

Dr. RALL. A small computer.

Mr. FLOOD. And you needed to renovate two rooms?

Dr. RALL. Small in capacity, but large in size. The new computers are large in capacity but small in size. We got this free so we thought it was worthwhile to take the space and alter the rooms to install it.

Mr. FLOOD. I hope you won't find out, like the Defense Department people tell us, that next week there will be a new generation of computer and this is obsolete.

Dr. RALL. This is technically obsolete anyway, but it provides our scientists the opportunity to actually work with a computer. Otherwise, we have to go through leased wires from our Institute in North Carolina to the Division of Computer Research and Technology in Bethesda. This allows them to have it in their own hands.

Other costs under "Other Services" are special animal services. Also, we are charged for data processing. This can amount to a significant amount. All of these are increasing.

Mr. FLOOD. Well, we will watch it, these other services, in all the Institutes. That same phrase is being used by everybody. It is quite an umbrella.

Mr. Obey.

Mr. OBEY. Thank you, Mr. Chairman.

Dr. Rall, first of all, let me say I am glad to see you here. Let me say, Doctor, although I was not there when you gave your statement, I read it afterwards, but I thought your speech on the Conference on Occupational Cancer in New York was one of the most thoughtful given. Your Institute deals with an important problem. We have a great devotion in this country to freedom of choice, but individual human beings really have very little freedom of choice in terms of the kinds of exposure they have to all kinds of agents in the environment which may or may not be harmful. They really have no control over events which are set in motion by new technology. I noted last night when I was going over the hearings of last year that Dr. Stetten said to me at that time, "What you have brought out, it seems to me, is the enormous acceleration in increasing the complexity of the tech-

nology in our environment, and that we are lagging behind in the biological investigations of its effects and dangers. We are not accelerating at the same pace in our biological investigation."

I would like to ask you a few questions to try to determine how much your budget really can contribute to the acceleration of those biological investigations.

I have a great number of questions. I am going to ask you to respond in the record to many of them in the interest of time. I know you did it in your statement but would you again very briefly and for the record define the mission of NIEHS as you see it? Would you explain how it differs from NCI, EPA, FDA, from NIOSH? Would you expand in the record, but for a very brief time here could you explain to me what you do that nobody else does?

Dr. RALL. We are concerned with the potentially toxic agents and factors in the environment. This means really the total environment. It includes exposures in the workplace. It includes exposures and possible synergistic effects of environmental agents and therapeutic drugs. It is the total interaction between man and potentially toxic agents in the environment. So one aspect of our uniqueness is that we cover everything. This is important because the other agencies have limited purviews.

Now, we differ from virtually every other NIH categorical Institute. NCI is simply typical of one of them although in many ways it is also atypical. They look at one viewpoint only, the development of cancer. We are concerned about a variety, the development of lung disease, kidney disease. We are concerned not about the end point, but the initiating agent, the chemical in the environment that is causing it. This is part of our uniqueness.

The other thing is that we are the only Federal agency that I know of that is actively developing new methods to better predict the toxicity of these varieties of toxic agents. We are trying to get better tests, tests that can be done more quickly and more inexpensively.

I think that is very briefly the sort of things that make us very unique.

COORDINATION WITH OTHER AGENCIES

Mr. OBEY. Would you explain for the record how you coordinate with NCI and EPA and the other agencies you coordinate with?

Dr. RALL. Yes, sir.

[The information follows:]

There are a wide variety of mechanisms available to insure effective interagency communications, cooperation, and collaboration. These range from formal coordinating groups, such as the DHEW Committee to Coordinate Toxicology and Related Programs, to less formal interagency groups designed to bring together scientists working in the same field, such as the Interagency Panel on Environmental Mutagenesis. Other avenues include widespread one-to-one contact between scientists, attendance at national and international scientific meetings, and constant review of the relevant scientific literature.

Additionally, the NIEHS—often in conjunction with other agencies concerned with environmental problems—sponsors a series of conferences whose purpose is to assess the present state of knowledge about, and possible human health impacts of, potentially hazardous environmental agents from a variety of sources. These conferences provide a forum for the open and direct exchange of information between scientists working on different aspects of the same scientific problems. Through its journal, Environmental Health Perspectives, the Institute publishes the proceedings of these meetings in order to insure maximum com-

munication of research findings. These conferences frequently result in the identification of new research directions to be undertaken by NIEHS and other groups concerned with environmental health problems.

Specifically, NIEHS and NCI are coordinating primarily in the field of environmental carcinogenesis. Both groups are represented on the DHEW Committee to Coordinate Toxicology and Related Programs and the Interagency Panel on Environmental Mutagenesis. Also, we participate in the Cancer Institute's Interagency Collaborative Group on Environmental Carcinogenesis.

Foremost among our interagency activities with EPA is our work on energy-related health effects research. We have been involved in this planning effort for the last year and we will soon begin research under an interagency agreement with EPA.

FORWARD PLAN

Mr. OBEY. Do you have a forward plan for fiscal 1976?

Dr. RALL. Yes.

Mr. OBEY. Would you supply that for the record and also supply me with a copy as well as anybody else in the committee who might want one?

Dr. RALL. Yes.

[The information follows:]

Forward Plan FY 1976 - 1980
National Institute of Environmental Health Sciences

I. MISSION

The National Institute of Environmental Health Sciences seeks to increase our understanding of environmental agents which can adversely affect man's health either immediately or over time. The results of the Institute's research are promptly made available to agencies having responsibility for environmental monitoring, standard setting, and control. The Institute seeks to determine the magnitude and significance of the hazard to man's health resulting from exposures to ranges of concentrations of chemical, physical, and biological agents in the environment. Underlying mechanisms of adverse response are examined in order to determine the principles and generalizations which can provide criteria which can serve as a basis for the establishment of standards by those agencies charged with the regulatory responsibility in this area.

Among the beneficiaries of the basic knowledge developed by the Institute are those professionals concerned with the environmental components of human disease--e.g., physicians treating poisonings by environmental chemicals; and medical teams concerned with the etiology of new diseases peculiar to certain locales or puzzled by drug interactions with environmental components. Our data are also useful to other programs dealing with environmental components of cancer, mutagenesis, or heart and lung diseases (e.g., National Cancer Institute, National Institute of Child Health and Human Development; National Heart and Lung Institute). Close liaison is maintained between the Institute and the academic and medical communities as well as with other Institutes at NIH. Liaison is also maintained between NIEHS and other Governmental agencies concerned with the environment--EPA, FDA, and NIOSH. Such contacts maintain awareness of programs, avoid unnecessary duplication of efforts, and foster supportive collaboration where feasible.

With the exception of ad hoc responses to emergent problems, it is anticipated that the mission of this Institute will change little over the period FY 1976-1980. Recent efforts, as will be described, have succeeded in redeployment of Institute resources to insure support of program segments and goals considered to constitute areas of high national priority.

II. PROGRAM BALANCE AND STRATEGY

With population expansion and the growth of technology, the problems of environmental contamination have become increasingly apparent. Electric power generating capacity in the United States increased over 20-fold from 1920 to 1969. There are now some 45,000 registered pesticide formulations on the Federal rolls. Synthetic chemical production has more than doubled in the last ten years. These and other circumstances have led to intense national concern. Some evidence of the depth of this concern is illustrated by the variety of recent reports calling attention to environmental health problems; among them, the well-known Gross (1962), Tukey (1965), Spilhaus (1966), and Linton (1967) reports. This national concern has led to a major reorganization of Federal efforts in a variety of ways and led, in particular, to the developmen

in 1968 of an entirely new unit within the National Institutes of Health, the National Institute of Environmental Health Sciences.

Unique among the NIH Institutes, the NIEHS focuses not on a specific body organ or disease end point, but rather upon a process -- the manner in which human health is adversely affected by chemical, physical, and other environmental factors. In addition, because the control of the environment is increasingly a governmental responsibility, be it Federal, state, or local, the Institute provides a health science base to the regulatory agencies.

The breadth of the Institute's mission far outstrips the resources available for its conduct. This will undoubtedly always be so. Thus, one of the major tasks confronting the Institute is that of careful problem selection.

This process has led the Institute to identify five major areas for particular emphasis:

1. Environmental health sciences centers
2. Environmental mutagenesis and reproductive toxicology
3. Etiology of environmental diseases and disorders
4. Environmental pharmacology and toxicology
5. Environmental pathogenesis

A characteristic of environmental health problems is that they require a broad spectrum of research efforts for their resolution. These efforts range, for example, from fundamental studies of how the body accepts substances and transforms them, singly or synergistically, into harmless or highly toxic compounds, to highly refined studies on the toxic effects of single compounds. For each of the areas enumerated above the entire range of both broad and specific studies are required. It is the far ranging nature of the problems faced by the Institute which demands the utilization of a wide range of program mechanisms for their resolution.

The Institute serves as a national focal point for environmental health research. Through various grants programs and collaborative and cooperative activities, the Institute supports and cooperates with those scientists and research teams which can make contributions to an understanding of the problems in this field. Through liaison and coordination activities, the Institute maintains close cooperative relationships with other Federal agencies working in this area.

III. OPPORTUNITIES FOR RESEARCH PROGRESS

Environmental Health Sciences Centers

The University-based Centers serve to integrate the efforts of scientists in several traditional disciplines and foster application of expertise across disciplincary lines to environmental health problems. The Centers are characteristically made up of groups of scientists who collaborate to develop fundamental and practical information about the causes and nature of environmental diseases in order to guide corrective and therapeutic programs. Because

of the variety and complexity of environmental problems, several centers with complementary spheres of interest are required to fulfill the national need. Accordingly, six Centers, each with special expertise in one or more of the major categorical programs of the Institute, are supported. Collectively, they provide outstanding capabilities in traditional basic and applied disciplines vital to the Institute program including, among others, chemistry, cell biology, genetics, physiology, biostatistics, pharmacology, toxicology, pathology, epidemiology, behavioral sciences, nutritional sciences, occupational medicine, and chemical and environmental engineering.

In the coming years the Institute plans the development of new centers in additional areas of particular importance to the continued development of the Institute's programs. Of particular importance are the areas of heavy metal toxicity and mutagenesis.

Environmental Mutagenesis and Reproductive Toxicology

The mutagenesis and reproductive toxicology program deals with environmental phases of reproduction and fetal development. It is aimed at interaction between chemical agents found in air, water, food and occupational situations and changes in the genetic makeup of man, his reproductive capability, and in the development of the embryo or fetus. Induction of permanent changes in human genetic material is without question the most profound danger associated with environmental agents. In addition to anatomical defects generally ascribed to mutations, it is clear that subtle deficits in mental capacity and susceptibility to degenerative and infectious diseases also result from genetic aberrations. A major obstacle in assessing mutagenic potential of chemical agents has been the lack of rapid, inexpensive test systems with unequivocal quantitative relevance to man. This program is designed to fill this gap and supports substantial efforts aimed at the development of sensitive test systems for detection and quantification of mutations.

Man's chemical environment is becoming increasingly complex. Every year an increasing number of new man-made chemicals are put into wide-spread distribution in the form of food additives, drugs, industrial compounds, cosmetics, insecticides, and herbicides. In addition to these compounds there are ill-defined mixtures that reach us in the form of atmosphere pollutants. Recent studies on some of these compounds, which are considered "safe" (approved by the FDA) for human use, have shown that they are mutagenic in various test systems. They break chromosomes and even produce gene mutations. This situation results from the fact that the testing procedures currently recommended to approve the use of a given compound by the regulatory agencies of the Government (such as the FDA) do not detect mutagenicity. That tests to evaluate the mutagenicity of compounds with wide-spread distribution in the human population are not mandatory is considered by many geneticists to provide a serious potential hazard for producing undesirable genetic effects in man. This is not only a problem for the present generation through chromosome breakage and mutation in somatic cells, but a problem for all future generations through the production of gene mutations and heritable chromosome aberrations. It is extremely difficult to establish the mutagenic effect of chemical compounds in man. Since direct tests of potential mutagens cannot and should not be made on man, we have to rely on tests with experimental organisms. These test systems range from microbes to mammals. An accompanying area of concern is the effect of environmental stresses on

reproduction and development. Although some of the biochemical mechanisms involved with teratogenesis overlap with those involved in mutagenesis, it is apparent that many biochemical explanations for teratogenic effects are unique. The effect of man's environment on his ability to reproduce, and produce normal offspring which develop normally, is of obvious importance.

Since the structure of DNA is the same in all organisms, there is every reason to expect potent mutagens in experimental test systems to be potent mutagens in man. It is a worldwide problem of utmost urgency to evaluate the toxic significance of these compounds in experimental test systems with regard to their relative hazard for man. New mammalian test systems have to be developed, including human cells in tissue culture, and the reliability of extrapolation from experimental test systems to man must be established.

It is becoming increasingly obvious that radiation contamination of our environment is just one component of a more general contamination. In fact, all of these stimuli are responsible for what we refer to as the "spontaneous background" of genetic damage. There are strict regulations regarding the use of radiation to avoid making any significant increase in the load of genetic damage in the human population. We must gain assurance that we are not ignoring "the submerged part of the iceberg," contamination of our environment by man-made chemicals, which may actually present a more serious hazard.

Etiology of Environmental Diseases and Disorders

The central objective of the etiology program is to establish causal associations between human diseases and environmental chemicals and physical factors. It includes broad surveys aimed at identifying chemical agents now in use, or proposed for use, that have adverse effects upon biological systems. Concomitantly, it deals with description of specific malfunctions produced by these agents in body organs. This research provides a sound basis for clinical recognition of environmentally-related disorders in man, determination of their causes, and implementation of correct therapeutic and preventive measures. In a broader sense, it generates understanding of quantitative relationships between human diseases and noxious environmental agents. This understanding will serve as a basis for rational management of current technology and future industrial development in such a way as to make them compatible with human health and well-being.

The study of the etiology of environmental diseases is one in which considerably more work needs to be done. The continuing lack of resources in the broad field of environmental health research has made it necessary to reduce the emphasis in the area in order to permit growth in new areas such as mutagenesis. This trend cannot continue if the total field is to flourish. Of particular importance is the area of epidemiology. In every field of environmental health research, there are important questions which require epidemiological investigation.

A relatively new field being developed is the area of physical factors (e.g. heat, light, noise, microwave, and laser radiation). Much work is required to develop this important area.

Environmental Pharmacology and Toxicology

The pharmacology and toxicology program is designed to develop understanding of the principles and mechanisms involved in toxicity of environmental agents. The research ranges from mechanistic studies of factors that alter the toxicity of chemical agents to studies on absorption and transport within the body. The nature and sites of defense systems and molecular targets associated with visible functional disorders are also being investigated. The goal is to provide a rational basis for maintaining, through environmental management, reasonable safety margins between environmental and body burdens of toxic agents in order to safegard human health now and in future generations. Of enormous importance is the development of better methods of screening and testing environmental agents.

Most scientists recognize that requirements for testing for interactions of a given product or chemical with other chemicals or products or contaminants of our environment cannot be left to industry without serious risks to industrial productivity. At present, the number of large scale programs seeking ways to study interactions, new methods to get answers, quicker or better ways to pick likely interactions, is essentially zero. What programs exist are largely the result of a single investigator's hobby or were set up to respond to a tragic accident or series of mishaps with a specific combination.

At present, environmental contaminant interactions with other components, like drugs, are the subject of limited studies at FDA, EPA, and NIH. Some studies are made at Pharmacology-Toxicology centers or university-based centers of the NIGMS and NIEHS grant programs. In few if any cases are any more than ad hoc approaches being used. No one has the time, staff, or resources to try to devise new methods to test for interactions or identify interactions with the exception of a program dealing with one possible result of such interactions, namely cancer. Only NCI has made even a limited start in this new direction. In all other cases it is a particular combination that is being tested by the old methods. The major problem here is that the old methods start to come apart when more than two components are being tested for an interaction. Sets of three or more chemicals pose problems seldom attacked in any laboratory.

Environmental Pathogenesis

The pathogenesis program focuses upon the details and time sequence of molecular and cellular events that culminate in recognizable diseases and endpoints upon exposure of individuals to toxic agents. Because of the wide range of chemical agents and physical factors present, no organ or body function can be considered invulnerable. Diseases of the pulmonary and cardiovascular systems, the liver, kidneys, reproductive system, digestive tract, the central and peripheral nervous systems, and degenerative disorders of complex and long-term etiology have been documented and related to one or more environmental agents. Additionally, the program is intended to clarify the interactions through which environmental agents play a secondary or ancillary role in the progress of degenerative disorders. Knowledge of initial or very early molecular and cellular lesions and understanding of their role in pathological endpoints offers the best hope, apart from prevention of toxic exposures, for detecting and countering the development of diseases before damage in target organs become irreversible and progressive. Much work is required if we are to gain a fuller understanding of the contributions of environmental gents to acute and chronic disease development.

Forward Plan FY 1976 - 1980

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Special Research Initiatives

I. General Program Development -- The National Institute of Environmental Health Sciences seeks to increase our understanding of environmental agents which can adversely affect man's health either immediately or over time. The results of the Institute's research are promptly made available to agencies having responsibility for environmental monitoring, standard setting, and control. The Institute seeks to determine the magnitude and significance of the hazard to man's health resulting from exposures to ranges of concentrations of chemical, physical, and biological agents in the environment. Underlying mechanisms of adverse response are examined in order to determine the principles and generalizations which can provide criteria which can serve as a basis for the establishment of standards by those agencies charged with the regulatory responsibility in this area.

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With the exception of ad hoc responses to emergent problems, it is anticipated that the mission of this Institute will change little over the period FY 1976-1980. Recent efforts, as will be described, have succeeded in redeployment of Institute resources to insure support of program segments and goals considered to constitute areas of high national priority. While it has been possible through this device to begin development of a small number of new research programs, e.g. mutagenesis and reproductive toxicology, it has been at the expense of other important research areas. The increasing number and variety of important research problems in environmental health dictate the orderly expansion of the Institute's programs.

II. Current Status and Plans for Future Activities -- Unique among the NIH Institutes the NIEHS focuses not on a specific body organ or disease end point, but rather upon a process -- the manner in which human health is adversely affected by chemical, physical, and other environmental factors. In addition, because the control of the environment is increasingly a governmental responsibility, be it Federal, state, or local, the Institute provides a health science base to the regulatory agencies.

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Looking toward the future, the Institute plans a continuation of a highly interrelated, coordinated program combining grants, contracts, and research conducted within its own laboratories. The broad areas spelled out in the program structure seem appropriate over the near term. The major problem which serves as an impediment to orderly development of the Institute's programs is the severe shortage of resources. In addition, and in contrast to the other NIH programs, the NIEHS has not experienced growth as a result of Congressional increases. In fact, the only increases which the Institute has received through Congressional action have been to restore the Institute's programs to previous levels of activity.

While the lack of financial resources has been a major brake on the Institute's development, the stringent manpower ceilings imposed on the Institute have had an even more deleterious effect. These ceilings have impeded the productivity of many of its scientists.

In addition, the lack of fiscal resources has prevented the Institute from rounding out its intramural research program and kept the Institute from awarding all but a few grant awards, and precluded the development of major new research areas through the grants mechanism.

III. Opportunities for Research Progress -- There are significant gaps in the knowledge required in all of the Institute's research programs. Time and again, it has been made very clear that regulatory actions taken in the field of the environment rest on an inadequate research base. Since much of the regulatory action in the environmental area results in major cost to industry, as well as to Federal, State, and Local governments (a cost which is passed along to the consumer and the taxpayer), it is important that these actions be based on sound data and evaluation of public health considerations. In both relative and absolute terms, the efforts to control the environment are outstripping the science base upon which those actions are predicated. The appropriate growth and development of the Institute's programs is an appropriate first step toward the closing of these multiple gaps in knowledge.

IV. Estimated Costs

FY 1976 -- $25,195,000

FY 1980 -- $42,710,000

Forward Plan FY 1976 - 1980

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Special Research Initiatives

I. Mutagenesis and Reproductive Toxicology -- The mutagenesis and reproductive toxicology program deals with environmental phases of reproduction and fetal development. It is aimed at interaction between chemical agents found in air, water, food and occupational situations and changes in the genetic makeup of man, his reproductive capability, and in the development of the embryo or fetus. Induction of permanent changes in human genetic material is without question the most profound danger associated with environmental agents. In addition to anatomical defects generally ascribed to mutations, it is clear that subtle deficits in mental capacity and susceptibility to degenerative and infectious diseases also result from genetic aberrations. A major obstacle in assessing mutagenic potential of chemical agents has been the lack of rapid, inexpensive test systems with unequivocal quantitative relevance to man. This program is designed to fill this gap and supports substantial effort, aimed at the development of sensitive test systems for detection and quantification of mutations. While this program is currently under development in the Institute, the amounts available are not adequate to permit its full implementation. Thus, while the words that follow are very nearly the same as those confined in the "core" Forward Plan, it is our view that they support a significantly increased level of funding.

II. Career Status and Plans for Future Activities -- Man's chemical environment is becoming increasingly complex. Every year an increasing number of new man-made chemicals are put into wide-spread distribution in the form of food additives, drugs, industrial compounds, cosmetics, insecticides, and herbicides. In addition to these compounds there are ill-defined mixtures that reach us in the form of atmosphere pollutants. Recent studies on some of these compounds, which are considered "safe" (approved by the FDA) for human use, have shown that they are mutagenic in various test systems. They break chromosomes and even produce gene mutations. This situation results from the fact that the testing procedures currently recommended to approve the use of a given compound by the regulatory agencies of the Government (such as the FDA) do not detect mutagenicity. That tests to evaluate the mutagenicity of compounds with wide-spread distribution in the human population are not mandatory is considered by many geneticists to provide a serious potential hazard for producing undesirable genetic effects in man. This is not only a problem for the present generation through chromosome breakage and mutation in somatic cells, but a problem for all future generations through the production of gene mutations and heritable chromosome aberrations. It is extremely difficult to establish the mutagenic effect of chemical compounds in man. Since direct tests of potential mutagens cannot and should not be made on man, we have to rely on tests with experimental organisms. These test systems range from microbes to mammals. An accompanying area of concern is the effect of environmental stresses on reproduction and development. Although some of the biochemical mechanisms involved with teratogenesis overlap with those involved in mutagenesis, it is apparent that many biochemical explanations for teratogenic effects are unique. The effect of man's environment on his ability to reproduce, and produce normal offspring which develop normally, is of obvious importance.

Since the structure of DNA is the same in all organisms, there is every reason to expect potent mutagens in experimental test systems to be potent mutagens in man. It is a worldwide problem of utmost urgency to evaluate the toxic significance of these compounds in experimental test systems with regard to their relative hazard for man. New mammalian test systems have to be developed, including human cells in tissue culture, and the reliability of extrapolation from experimental test systems to man must be established.

III. Opportunities for Research Progress -- While the number of new agents being introduced into the environment is increasing each year, work aimed at developing systems to test the possible mutagenicity and teratagenicity is not keeping pace. It is critical that the work aimed at developing a basis for new assay and test systems be increased in both breadth and scope. It is important to expand the work aimed at developing a better understanding of the mutagenic and teratagenic process.

Forward Plan FY 1976 - 1980

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Special Research Initiatives

I. Energy -- In response to what has come to be called the energy crisis, and at the request of the President, the Chairman of the Atomic Energy Commission carried out a study aimed at development of an integrated energy research and development program for the Nation. Contained in the report of the study are a series of proposals aimed at the establishment of the capability to determine and control effectively the environmental and health insults from the energy system. The President's Budget for 1975 contains an increase of $133,700,000 for Environmental and Health Effects Research. In addition, $82,300,000 is requested for basic research and manpower development. Because of the pressure of time associated with "locking up" the President's Budget, most of these amounts were included in the Environmental Protection Agency's budget. An Interagency Committee has been established under the aegis of the Office of Management and Budget to allocate these funds among the many agencies which have responsibilities in this area. The Director of the National Institute of Environmental Health Sciences is one of the two HEW representatives on the OMB Interagency Committee.

II. Current Status and Plans for Future Activities -- Because of the fluid nature of the Executive Branch plans for attacking this important public policy problem, it is difficult to describe the current status of this area with precision. In general, however, the current status is that the Institute has developed a preliminary plan based upon a central role for the DHEW through the NIEHS in the health aspects of the energy crisis.

There are three major reasons for conducting energy-related environmental health research:

A. To help policy decision-makers choose among the wide range of available energy options available to them by providing data regarding the risk benefits of each.

B. To help reduce the health hazards associated with the options selected.

C. To validate the use of the options selected and to serve as a warning system in the event one of those options proves to be more hazardous than forecasted.

The general plan is to conduct and sponsor comprehensive field and basic studies on noxious agents associated with the development, use, and conservation of energy. The information developed will serve as a realistic base for regulatory action and for the practice of preventive and corrective medicine.

III. Opportunities for Research Progress -- There are a number of areas requiring investigation in the near term. These are grouped into the two broad areas of field and laboratory studies. They are grouped as follows:

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A. Field Studies
   1. Physical and Chemical Characterization of Hazardous Substances
   2. Epidemiclogical Studies
B. Laboratory Studies
   1. Physiology, Pharmacology and Toxicology
   2. Protective Mechanisms: Toxication, Detoxication, Distribution and Excretion
   3. Pathogenesis Mechaniams
   4. Behavioral Effects of Environmental Agents
   5. Mutagenic, Teratogenic, and Reproductive Effects

IV. Estimated Costs

FY 1976 --- $11,000,000

FY 1980 -- $15,000,000

BUDGET REQUEST FOR FISCAL 1976

Mr. OBEY. What was your budget request for fiscal 1976 when it left your shop to go to HEW?

Dr. RALL. $42,726,000.

Mr. OBEY. What level was it when it left HEW?

Dr. RALL. $35,676,000.

Mr. OBEY. And as it came out of OMB, it is what?

Dr. RALL. $31,113,000.

Mr. OBEY. It compares with last year now?

Dr. RALL. Last year was just under $35 million.

Mr. OBEY. The chairman got into this somewhat. Can you tell me what the results of those cuts will be in grants and contracts?

Dr. RALL. Very briefly, we will not be able to meet all of our continuing commitments. We will not be able to fund many of our important contracts. We will only be able to support 13 new research grants for the entire year.

Mr. OBEY. And you had to cut back on how many existing grants?

Dr. RALL. I don't think we are in a position yet to say how many. We are still calculating that out. We can supply that for the record.

[The information follows:]

It appears that we will not be able to support approximately 61 existing grants.

PERCENTAGE OF APPROVED GRANTS

Mr. OBEY. What percentage of approved grants can be funded under your budget?

Dr. RALL. If we are lucky, 10 percent.

ASBESTOS STUDY

Mr. OBEY. You mentioned the Duluth-Superior Asbestos study which this committee was kind enough to insert in the budget last year at my request.

As you know, I represent that area, at least on the Superior side. We are the side that doesn't have the plant. We don't have the tax revenue from Reserve Mining. We just have the problem which results. What is the status of that asbestos study? Did you say in response to the chairman that there was not money in the budget this year for it?

Dr. RALL. Next year. We will get the contract initiated this fiscal year. There will be no money in fiscal 1976 to continue.

RESEARCH CENTERS

Mr. OBEY. That does not make very much sense to me. What about the Research Centers? Would you just insert for the record what you do, what the general area of concentration is at each of the centers?

[The information follows:]

ENVIRONMENTAL HEALTH SCIENCES CENTERS

Title of Center	Location	Director	Area of Concentration
1. Center for Study of the Human Environment	University of Cincinnati	Dr. Raymond R. Suskind	Toxicity of heavy metals and toxic components of coal
2. Occupational and Environmental Health	Harvard University	Dr. James L. Whittenberger	Toxicity of a variety of occupational and environmental chemicals
3. Environmental Agents in Relation to Human Health Effects	Mt. Sinai School of Medicine	Dr. Irving J. Selikoff	Correlation of occupational exposures with health risk
4. Center for Environmental Management	Oregon State University	Dr. Virgil Freed	Agricultural products and pesticides and exposure to man
5. Research in the Environmental Health Sciences	N.Y. University Med. Center	Dr. Norton Nelson	Air toxicology, carcinogenesis, and occupational exposures
6. Center in Environmental Toxicology	Vanderbilt University	Dr. Robert A. Neal	Toxicology, pesticides and natural products

Many of these Centers have complementary spheres of interest because of the variety and complexity of environmental problems.

TRAINING

Mr. OBEY. Could you tell me just a bit about training?

What did you ask for for training funds when the budget left your shop?

Dr. RALL. Training, Mr. Obey, is such a confused matter presently.

Mr. FLOOD. That is the understatement of the morning, I will tell you that.

Dr. RALL. Well, it seems to me I have a couple of options. I can say I don't know. I could refer it to Dr. Lamont-Havers. We are very concerned about training because we see in this specific area a very great lack of properly trained scientists. I am very hopeful, however, that the National Research Council and the National Academy of Sciences study which is underway will identify the broad area of toxicology and epidemiology as one of the major needs of the country.

Perhaps then we can proceed with a rational training program.

Mr. OBEY. When NIOSH was before us, they painted some quite startling gaps between numbers available and numbers needed between toxicology, pharmacology, and the like. I assume you agree.

Dr. RALL. Absolutely.

IN-HOUSE RESEARCH

Mr. OBEY. Turning to in-house research, does your budget for in-house research allow for any real program increase?

Dr. RALL. No; it does not.

Mr. OBEY. How about any staff increase?

Dr. RALL. No; it does not.

Mr. OBEY. What is the thrust of your in-house research?

Dr. RALL. I think the most exciting thrust is involved in this ability now to use these simple microorganisms, one-cell organisms, mammalian cells, in conjunction with what we call metabolic activation, to predict very reasonably for such effects as carcinogenesis.

We are able to mix the chemical with the cell and then add to that mixture isolated enzymes from a rat liver or a rat lung which will metabolize the added chemical in much the same way as it is metabolized in the whole body. This lets us do in a test tube a study which would cost thousands more if it had to be done in a whole animal or a whole series of rats and mice. This, we think, is terribly exciting and terribly important.

TESTING FOR TOXICITY AND CARCINOGENICITY

Mr. OBEY. What kind of testing do you do for toxicity and carcinogenicity? What is involved in it? What is the cost? What is the average cost on those tests?

Dr. RALL. The standard full investigation of a new compound should include a month or two of so-called subacute study where the compound is fed to a series of animals for 1, 2, or 3 months. They are followed biochemically and then they are autopsied and tissue damage is looked for. This might cost $10,000, $20,000, or $30,000. After that comes the carcinogenicity study which is a 2-year study.

The animals are exposed for 2 years. This should be done with both mice and rats or some other combination of two species. The tissues are

then all looked at by a pathologist. This study will cost about $200,000 and take about 3 years.

Mr. OBEY. I know it is very hard to put a meaningful figure on this but what is the field you are talking about in terms of the number of chemicals or just the number of new chemicals coming into play each year?

Dr. RALL. There are probably about 250,000 chemicals a year synthesized, added to a base of about 3 million chemicals.

Those are laboratory curiosities. In terms of chemicals, we are exposed to and live with there are about 15,000 in the environment today. These are being added to at the rate of between 500 and 1,000 a year. That is between 500 and 1,000 new compounds enter the environment every year. Most of these, the great majority of these, have not been subject to toxicity testing.

Mr. OBEY. If you are just talking about 15,000 to 20,000 chemicals, those are the most prevalent and it cost you on the average of $200,000 apiece—you put the sum in the record, I am not a mathematician, that is why I am on this committee—but that is a tremendous amount of money.

Dr. RALL. Can our budget officer make that calculation? We will put it in the record.

[The information follows:]

It would require between $3 billion and $4 billion to test those chemicals that are already in our environment.

Mr. OBEY. I am intrigued by the new testing method you mentioned in your statement and in your conversation with the chairman. It would seem to me that is a pretty important item. How much is in the budget for next year for development of those new cheaper testing systems?

Dr. RALL. It is $1 million to $2 million.

Mr. OBEY. As contrasted to what would be a figure in the billions if we were to develop test methods for all these chemicals.

In your professional judgment how much could you use effectively for developing those new types of tests?

Dr. RALL. I think we could effectively use an additional $2.5 million for in-house research, and this, of course, would need to be accompanied by positions to be effectively used. I think the contract program could use an extra $1.5 million in this new test method development and similarly about $1.5 million in grants.

Mr. OBEY. What about for all test development, not just the new shortcut program? What do you have in the budget and what in your professional judgment could you use?

Dr. RALL. If you are talking about the entire spectrum of tests, probably four times what I mentioned, more like $4 million to $8 million, and I would think in terms of additional resources needed, about the same, a couple of million dollars in in-house research and a million and a half in contracts and grants.

TOXIC SUBSTANCES ACT

Mr. OBEY. As you will recall, Congress last year failed to pass the Toxic Substances Act. That act requires a number of things. It requires industry to prepare a list of all the chemicals they manufacture. It requires them to list public health and safety data pertaining to those

chemicals, and it provides, at least as I understand the bill, that industry must screen suspected chemicals before they go into the marketplace.

I suspect—at least I hope— the Congress is going to pass the Toxic Substances Act this year. It would seem to me that it would be critical, if that act is going to make much sense, for us to rapidly develop this new shortcut, low-cost testing system you are talking about, and I would also think that the availability and the adequacy of testing systems would be the cornerstone of regulations laid down by EPA and anybody else in town.

At the cost of $200,000 a test, if that is the average cost of the present tests, it would seem to me that that would represent a tremendous cost to industry and because of the tax writeoffs involved a tremendous potential revenue loss for the Government as well.

I would, therefore, think that it is absolutely crucial and in the interest of both industry and the public which is exposed to all of those agents that your program proceed at the fastest possible rate.

I don't think you would disagree with that statement, would you?

Dr. RALL. I would not disagree.

VINYL BROMIDE

Mr. OBEY. I notice this ad in Chemical and Engineering News on vinyl bromide. I don't know much about it but I do understand that that is a chemical very closely related to vinyl chloride. Is that true and has it been tested sufficiently?

Dr. RALL. That is true, vinyl bromide appears to us to be a close relative of the vinyl chloride, and it has not to our knowledge been tested adequately at all.

The fact that it is a close relative, I think, illustrates the need to understand the structural chemical relationships between compounds and to determine which are related to the other so you can generalize about potential toxicity.

There has been one short-term toxicity test on vinyl bromide. If you look at it chemically there is reason to believe it will be even more reactive than vinyl chloride and therefore potentially more toxic.

At one of our centers at New York University a study on vinyl bromide is beginning. We have a short-term test begun on vinyl bromide at our laboratories in North Carolina. The National Cancer Institute has vinyl bromide on its list to be tested, and industry is discussing the development of a contract with a private laboratory to begin testing in perhaps June or July.

But this compound has been on the market and is being intensively advertised.

Mr. OBEY. As I understand according to this ad, they are developing new carpets laced with it, new children's sleepwear laced with it. It would just seem to me again that that is something which we can't afford to let loose on the market without adequate test.

NOISE RESEARCH

Let me turn to last year's hearings for just a few moments before I get on to some other questions.

You referred to $2 million or $3 million in health research. You said, although we had about $100 million more research on noise, that there was only $2 million or $3 million in health research on noise levels, and you referred to a small $350,000 program that you had.

Do you know how much you will be able to spend on that this year?

Dr. RALL. We will spend a little bit more this year, perhaps $430,000, on noise research.

PETROCHEMICAL INDUSTRY

Mr. OBEY. Also, somewhat related to an earlier question the chairman asked, in the hearings last year you discussed the potential health problems associated with the petrochemical industry, with fossil fuels.

Would you just for the record list some of the health concerns associated with things like coal gasification, shale oil, and tar sand, problems with heavy metals, and the like?

Dr. RALL. Yes; we will put it in the record.

[The information follows:]

Before listing NIEHS' concerns with these various alternative technologies for energy production from fossil fuels, it is necessary to say that it is imperative that environmental health scientists be involved in the early stages of process development. At this stage, it is much easier to modify a particular process so that adverse impacts to the environment are reduced to their lowest levels.

Mining coal is known to be a hazard with regard to silicosis when the silica content of the coal vein is considerable. The mining of soft coal associated with lesser silica contents is notorious for its association with coal workers' pneumoconiosis in some geographic areas. Conversion of bituminous coal, by distillation, to coke with the concomitant production of coal tar is associated with the production of neoplasms of the skin, lung, larynx, nasal sinuses, kidney, bladder, stomach, intestine, pancreas, and blood forming organs as a result of exposure to the coal tar aerosols. Coal gasification is equally hazardous. Increased incidences of lung, bladder, and scrotal cancers have been demonstrated in gasworkers. Little is known regarding the toxicologic aspects of coal liquification or its effect on human health. It is expected that these liquid fuels contain polycyclic aromatic hydrocarbons, in addition to other chemicals, which have been suggested as playing a role in the etiology of pulmonary and cutaneous cancer as well as other skin disorders.

Combustion of the coals, liquified coal products and coal derived gas produce emissions containing oxides of nitrogen and sulfur, aliphatic and polycyclic aromatic hydrocarbons as well as a number of toxic metals. Coal gasification processes remove sulfur from coal. The environmental health concern associated with this removal process is the release of SO_2 to the atmosphere. Knowing that this substance is hazardous to health, it would be unwise to fail to develop methods for its removal following combustion by the new, more efficient economically useful methods.

The mining of oil shales and the production of shale oil for combustion and lubrication purposes may be even more hazardous. Pneumoconiosis is associated with the mining of different oil shales. Skin neoplasms of the scrotum have been reported in association with the use of shale oils as lubricants. Shale oils from Scotland, Estonia and Colorado have been demonstrated to be carcinogenic. The polycyclic aromatic hydrocarbons have been considered as the etiologic or coetiologic agent responsible for the neoplasms seen in exposure to shale oil. In addition to shale oil, shale paraffins, pitches, tars, and soot have been demonstrated to contain carcinogenic materials. Combustion of shale oil produces emissions which also contain polycyclic aromatic hydrocarbons, NO and SO_2. It is also known that the quantities of NO and SO_2 produced in the combustion of shale oil is greater than that obtained from coal. Oil shales are known to contain much greater quantities of nitrogen and sulfur than do coals. Combustion of shale oils represents a greater potential hazard with regard to the quality of the environmental air and increases the occupational health risks. Much research needs to be done on process modification and solid waste practices for oil shale extraction.

Heavy metals such as lead, cadmium, and mercury are widely distributed throughout the environment as the result of soil erosion and industrial and agricultural processes. These elements constitute a very important group of environmental toxicants since they are potent metabolic poisons to plants, animals, and man. Several scientists are developing basic information about the sites and mode of action of heavy metals. Special attention has been given to mercury and lead and their compounds, and the neurological and teratogenic effects of these substances.

INSULATION

Mr. OBEY. How about insulation.

Also last year you said, "We know very little about the toxicity of rock wool fibers and fiberglass."

Do we know much more this year than last?

Dr. RALL. We know little more this year. We are cosponsoring a meeting with the National Cancer Institute and the Thermal Insulation Manufacturers Association on the potential hazard of fine fiberglass. Dr. Selikoff is conducting some preliminary work on these hazards and we hope to have more information.

Mr. OBEY. How much is being spent in your shop this year on insulation materials?

Dr. RALL. Most of that would be on asbestos. We are spending about $1.7 million on insulation materials, primarily asbestos.

Mr. OBEY. Would you also place in the record, unless this is duplicative of the chairman's question, your concerns about the whole petrochemical industry and the items I did not mention earlier and how much you are spending on that and what you are spending it for?

Dr. RALL. Yes.

[The information follows:]

The subject of petrochemicals is so extensive and involves so many hundreds of chemicals that this subject must include a major portion of the synthetic organic chemical industry. There are a few major starting materials or feetbacks which are then converted by chemical reactions to end products such as fertilizers, plastics, fibers, rubber, paints, lubricating oil additives, pesticides, and solvents, to name a few. Therefore, this industry encompasses the occupational and environmental health problems associated with productions, use and disposal of products of this industry. The Institute is concerned with the mechanism of toxicity due to chronic exposure to environmental chemicals. Therefore, it is quite necessary to know what people are potentially exposed, by what route, and at what levels. The petrochemical industry by my definition is a major source of exposure to organic chemicals.

The major starting materials or basic chemicals derived from petroleum factories are ethylene, propylene, butylenes, benzene, toluene, and the xylenes. The number of products derived from the basic chemicals is numerous. The number of sources of occupational exposure to individual chemicals, as well as of the release of organic chemicals to the environment, is very large. There is a concern for exposure occupationally and as a result of release to the environment during processing, use and waste disposal, to individual substances, and to a large number of derived and combined substances.

Environmental health problems are associated with release of chemicals into the environment during production and waste water treatment. In organic chemical production, many undesirable side reactions can occur. These reactions are generally recognized, and equipment is designed to minimize their rate of formation. Even so, there are notable examples of toxic materials which are contaminants of chemicals or are waste water problems. In many cases, liquid effluents from industrial processes are not well characterized chemically or are difficult to characterize. Prudent control strategies to minimize release of potentially hazardous chemicals into the environment would include identification and segregation of problem waste streams. In this manner, the removal process is expediated and possibly a growing solid waste management problem is reduced to more manageable proportions.

Approximately 20 percent of NIEHS' budget could be tied to research on petrochemicals due to their broad ramifications. Specifically, the extramural grants programs supports work on vinyl chloride, vinylidene chloride, haloethers, and the movement of chemicals such as pesticides in the terrestrial environment. Intramural programs include inhalation studies with vinyl chloride and other commercially important organic chemicals; uptake, distribution, and metabolism of hydrocarbons by marine organisms; metabolism of pesticides; and uptake distribution and metabolism of impurities of pesticides (i.e., dioxins in 2,4,5–T).

In addition, intramural programs are designed to produce rapid screening programs to indicate potential mutagenicity of organic chemicals. Such techniques would be very important in implementing the Toxic Substances Control Act.

U.S.-U.S.S.R. HEALTH AGREEMENT

Mr. OBEY. Also I recall when you testified a year ago we had some Russian scientists in the back of the room who were here with you that day. Would you just supply also for the record some information about the U.S.-U.S.S.R. health agreement.

Describe some of the things you are working with them on, and your evaluation of how productive that is.

Dr. RALL. We shall do that.

[The information follows:]

Joint research efforts under the U.S.-U.S.S.R. Cooperative Health Agreement have entered their third year. The first year was concerned largely with establishing working relationships and areas for joint study. Initiation of cooperative research efforts began in the second year of the agreement and involved exchange visits between scientists of both sides. In December 1974, American and Soviet researchers participating in the agreement met at the invitation of the Soviet Government in Riga, Latvia, to present the results of their cooperative effort to date. The results of this symposium will be published in 1975 in both the United States and the Soviet Union.

A cooperative research program for 1975–76 was agreed upon during the Riga symposium. Research efforts are divided into three problem areas which seek to explore the methodological basis for assessing the biological efforts of chemicals which might be inhaled, or introduced orally, or both simultaneously. Some of the research projects which will be conducted in 1975–76 include a comparison of approaches to studying the effect of specific pollutants on the behavior of animals and humans; improving the scientific basis for extrapolating laboratory animal data to man; developing more rapid methods to predict the toxic effect of chemicals; and studying the embryotoxic and teratogenic action of certain pesticides.

The American participants in the cooperative program are generally quite satisfied with the progress being made in the joint research areas, recognizing the trailblazing nature of the developing relationship with their Soviet counterparts. Scientists on both sides have contributed considerable time and effort to establish working and personal relationships which overcome language differences, distance, red tape, and social and professional perspectives. The fact that by the end of 1975 over 20 scientific papers will have been published by American and Soviet scientists on environmental health research conducted under the auspices of this agreement demonstrates the contribution of this effort to the protection of many from the harmful effects of environmental agents.

AEROSOL SPRAYS AND FREON

You also mentioned last year the whole question of aerosol sprays and freon. How do you determine between you and EPA, for intsance, how you deal with questions like that?

Dr. RALL. Well, with the freon problem I don't think anyone had realized that freon was seriously involved in ozone destruction and ultraviolet carcinogenesis. I am very pleased that one of our major grantees, Dr. Frederick Urbach at Temple University, has been working on the problem of ozone as affected by freon and what this does to human health, and in fact his biological data were the primary source of biological information in the climatic impact assessment program that the Department of Transportation began about 2 or 3 years ago, to assess the effect of the SST, so when the ozone-freon problem became apparent, Dr. Urbach, whom we have supported for many years now, is really the prime expert in that area.

In terms of areosols in general, a variety of agencies are involved—the Consumer Product Safety Commission, the Food and Drug Administration, as well as ourselves and EPA. We work together very closely in this. There are so few facilities for inhalation toxicology, and we have some of the best in the world, that the problem really is not overlapped but gaps.

PERSONNEL

Mr. OBEY. Let me ask a couple questions about personnel. You have 240 positions and no new ones requested in the budget; right?

Dr. RALL. That is right.

Mr. OBEY. How can you reasonably expect to accelerate your new test development program with no new positions?

Dr. RALL. It will be very difficult. We will try to do it through the various other mechanisms, contracts and grants.

Mr. OBEY. I know you have space problems. Within your space limits, in your own professional judgment, what additional personnel could be utilized in your shop?

Dr. RALL. We think with crowding we could effectively use another 50 people.

Mr. OBEY. Did you say 15 or 50?

Dr. RALL. Fifty. They would be crowded but I think it would work.

PERMANENT FACILITY

Mr. OBEY. I don't want to take much more time. I would like to put a series of questions in the record on your building problem down there and ask you to respond to them.

I would also like to ask you when you do respond to these questions I would like you to explain what the square foot cost would be for that building that you have been thinking about for years and why it would be so high.

Dr. RALL. I shall.

[The information follows:]

The gross square foot costs for our permanent facility is approximately $143.00. The reason this appears to be high is because this Institute will be absorbing a substantial portion of the site development cost for the 509 acres. This site development will help accommodate other agencies who plan construction on this site in the future. When the cost of site development is deducted, this cost is comparable to construction costs for other basic research laboratories. The nature of the Institute is such that it will require highly sophisticated facilities with a great deal of mechanical capability to insure continuity of experimental work, especially in animals.

REPORT ON UTILIZATION OF FEDERAL LABORATORIES

Mr. OBEY. I want you to expand more for the record as well, but for my own benefit now let me just ask you one last question.

As you know, the Subcommittee on Agriculture—Environmental and Consumer Protection had prepared for its use an investigative report on the utilization of Federal laboratories.

I would like you to respond to that report for the record but let me just quote two things specifically from it. On page 75 it said:

A similar hazard substances program, probably identical in many respects to the above program—for your shop—was also identified by the National Institute for Occupational Safety and Health as substantially contributing to its need for a new facility in the Cincinnati, Ohio area.

Then it went on to say a little later that——

Although it is currently projected that a permanent facility could be occupied by fiscal 1980, it is also projected that personnel would have reached only the 800 level. Therefore, at the time of beneficial occupancy the permanent facility, according to an institute official, would only be half staffed.

Then they go on to say:

This, in the opinion of the investigative staff, certainly represents an example of planned-over building.

What is your response to that?

Dr. RALL. Our response is that we respectfully disagree with that staff report.

Mr. OBEY. Why?

Dr. RALL. Certainly there are areas of similarity between our mission and the Occupational Safety and Health Institute, but occupational health is only one subset of environmental health.

They are, for instance, involved in safety problems, which is not within our purview. They tend to be involved in occupational settings with much higher concentrations of chemicals for shorter periods of time than we are in the environmental area.

Again I think there is need here for simply effective coordination. There is no duplication and overlap between our institute and theirs.

In terms of the planned-over building, this does concern me very greatly indeed. The sort of problems that we discuss around this table every year, the proliferation of chemicals from the petrochemical industry, from the new energy sources, from the expanded use of old energy sources, these have really only begun to occur in the last 20 years or so.

We will begin to see the long term effects of them over the next decade, and it seems to me absolutely vital that we must be prepared to respond to them. We have lived through problems with mercury toxicity to the nervous system, lead toxicity to the nervous system, asbestos disease, lung problems, and carcinoma problems.

The polychlorinated biphenyl toxicity is well known. Cadmium, the problem of dioxins, which were a major threat to causing damage to offspring, these are all examples that have occurred in the last 4 or 5 years, and it just seems to me inconceivable that we don't have many more such examples in the next 5 or 10 years and I feel we must be prepared to attack and solve these problems in the future.

Mr. OBEY. Thank you.

That is all, Mr. Chairman. Thank you.

Mr. FLOOD. Mr. Roybal?

HAIR DYES

Mr. ROYBAL. Doctor, I have been reading your testimony of last year and that of this year and I am very much impressed, but somewhat frightened, that is, frightened by the prospect that there are so many things that still have to be done to protect the general public that a lay person like myself seems to see no end to.

However, the work that you are doing is most commendable and I would like to compliment you for your efforts in this field.

One of the things that immediately came to mind when I was thinking about the public in general is a very simple little statement that nevertheless hit home, and that is that, almost all commercially avail-

able hair dyes are genetically active in newly developed short term tests.

Then you go on to say that you don't know whether or not there is any cancer involved with it. Very frankly, most women do use dyes. Many men do, too, so it isn't just something that women use. It is something that men are continuing to use more and more.

How much money is spent in trying to determine whether or not these dyes can eventually cause cancer?

Dr. RALL. This problem is such a new problem that I really can't give you good answers like that yet. This really only became apparent less than a month ago.

Dr. Bruce Ames from the University of California at Berkeley reported this in the proceedings of the National Academy of Sciences. We are working very hard to check these results in a variety of other systems and as of right now these hair dyes are being looked at in eight or nine other test systems for mutagenic activity. We hope these will be able to give us a firmer basis to suggest that they are human health hazards or not.

Certainly this is a problem of potentially very large proportion. We are working with the Cancer Institute. They are beginning to test some of these hair dyes now for carcinogenicity, but this will be in the regular 2- to 3-year test and it will be a long time before we know.

One of the problems is that the hair dyeing process is very complex. In the two-solution way of dyeing hair, which is the common way, you mix the hair dye with hydrogen peroxide and the hydrogen peroxide reacts with the hair dye and causes a formation of a variety of different compounds.

Now, it is these different compounds that may be mutagenic and they have not been tested, so we are very concerned about this. Twenty million people, mostly women, dye their hair regularly and are exposed to significant amounts of compounds that are active in this one system and we think we must move on this as fast as we can.

Mr. ROYBAL. Would you expect them to be spending more money in this research in years to come than you have in the past?

Dr. RALL. Yes, we expect to.

Mr. ROYBAL. And you will probably be budgeting for such an eventuality?

Dr. RALL. That is right.

Mr. ROYBAL. Are you now budgeting for that?

Dr. RALL. Yes; we are trying to do a modest amount of reprogramming to begin to fill the need that we see specifically with the hair dyes.

Mr. ROYBAL. One thing that got my attention was the phrase, "Almost all commercially available hair dyes," and I said to myself there must be some that are not causing cancer and why doesn't your department tell us which are not? Then I went on to read and found out that you still don't know which are potential carcinogens. That means then that the field hasn't been exactly studied to the point where you can definitely say that these dyes are or are not dangerous.

Dr. RALL. This is a very new finding. Dr. Ames went out to two drugstores in Berkeley, California, and was able to find 168 separate hair dyes and of those, 150 were positive. I don't have the list of which were positive and which were negative, but I think it is too early for that information to be meaningful.

Mr. ROYBAL. It still wouldn't make any difference if we did have it at the moment.

Dr. RALL. No.

Mr. ROYBAL. You don't have the full answer. You still may be wrong if you do recommend one over the other.

Dr. RALL. That is right.

Mr. ROYBAL. So it will take about 3 years, you say, before an answer can be given?

Dr. RALL. I think we can do it more quickly than that. I think if we can look at the whole battery of these short tests, of which there are about 8 or 10, we can get a much better idea of whether this is an unusual quirk or strange quirk or whether it is a consistent pattern.

If it is a consistent pattern, I think this could be a public health hazard of major proportions and we will try to let people know.

Mr. ROYBAL. Thank you, Doctor.

Dr. RALL. Thank you.

Mr. FLOOD. Just one question on that. You have a hair dye and it produces cancer. The hair is on the top of your head. It produces cancer. How? You were talking about genetic hair dyes. How is it going to get into the system?

Dr. RALL. Absorbed through the scalp. About between a half and 1 percent, and there are experiments which show this, of the hair dye that is added appears in the urine, so somewhere around a half to 1 percent is absorbed through the skin on the scalp and this is known.

Mr. FLOOD. Absorbed through the skin?

Dr. RALL. Through the skin and through the body.

Mr. FLOOD. Mr. Natcher.

Mr. NATCHER. Dr. Lamont-Havers, can you tell me if sometime during the year of 1973, which of course was prior to your time, along about January 1, if at the request of the Senate Appropriations Committee a report was prepared and submitted to the committee concerning the number of people in this country who had deadly or serious diseases and there was nothing they could do about it? Do any of you gentlemen know anything about a report along this line?

Dr. LAMONT-HAVERS. Yes, Mr. Natcher, I remember, because at that time each of the Institutes prepared a table showing the diseases with which they were concerned and estimates with regard to the numbers affected, the economic impact, et cetera.

Mr. NATCHER. Yes.

Dr. LAMONT-HAVERS. Having said that, sir, I am not quite sure just what's happened since then, but we can certainly find out.

Mr. NATCHER. Doctor, if you would, at this point in the record, unless that report is voluminous, and you might want to submit it to Mr. Neil here on our committee, who will use his good judgment, at the approval of my chairman, Mr. Flood, I would like to have that inserted in the record. I understand it is just a page or two; very short.

Dr. LAMONT-HAVERS. There were tables rather than a report; figures rather than explanatory text. I think the table as far as my memory serves me was only a page or two. You are right. I don't think it is that great.

Mr. NATCHER. It won't require much space and if you would submit that, Mr. Chairman, with your approval to Mr. Neil I would like to have that placed in the record.

[The information follows:]

NATIONAL INSTITUTES OF HEALTH

1975 and 1976 Program Areas of Special Concern
(All columns except 5 & 6 in thousands)

Appropriation/Program	1974 Actual Obligations (1)	1975 Estimated Obligations (2)	1976 Budget Request (3)	No. of People Afflicted (4)	Life Expectancy of Afflicted (5)	Years of Life Lost Due to Disease (6)	Loss to Economy GNP (7)	Loss to Economy Fed. Taxes (7)	Data Furnished by Private Agencies (8)
National Cancer Institute[1]									
Nutrition	$2,700	$4,300	$2,800	xxx	xxx	xxx	xxx	xxx	xxx
Cancer task forces	23,239	27,415	26,730	xxx	xxx	xxx	xxx	xxx	xxx
Smoking and health	7,420	8,600	8,000	xxx	xxx	xxx	xxx	xxx	xxx
Cancer research centers	80,715	115,834	100,699	xxx	xxx	xxx	xxx	xxx	xxx
Cancer control	34,055	50,098	45,156	xxx	xxx	xxx	xxx	xxx	xxx
Cancer construction	27,550	38,000	22,000	xxx	xxx	xxx	xxx	xxx	xxx
Combined treatment modalities	37,357	50,967	45,000	xxx	xxx	xxx	xxx	xxx	xxx
Pap testing	(---)	(8,870)	(8,000)	xxx	xxx	xxx	xxx	xxx	xxx
Breast cancer detection and treatment	(---)	(31,083)	(26,083)	xxx	xxx	xxx	xxx	xxx	xxx
National Heart and Lung Institute									
Arteriosclerosis	121,274	132,540	121,600	26,000	70 yrs.	11	$7,100,000	$300,000	N.A.
Pulmonary disease	41,445	50,822	43,550	11,000	N.A.	N.A.	800,000	100,000	N.A.
Blood resources and thrombosis	33,469	39,068	33,820	1,800[2]	N.A.	N.A.	N.A.	N.A.	N.A.
Sickle cell diseases	16,000	16,000	16,000	50	30 yrs.	34	N.A.	N.A.	N.A.
National Institute of Dental Research									
Dental caries	8,886	10,900	8,420	95% pop.	N.A.	N.A.	24,400	6,100	N.A.
Periodontal and soft tissue diseases	10,447	11,200	9,078	83% pop.	N.A.	N.A.	73,300	18,300	N.A.
Craniofacial anomalies	7,934	7,600	6,098	60% pop.	N.A.	N.A.	75,000	19,600	N.A.
Pain control	1,000	1,600	1,435	98% pop.	N.A.	N.A.	N.A.	N.A.	N.A.
National Institute of Arthritis, Metabolism, and Digestive Diseases									
Cystic fibrosis	2,499	2,367	2,417	30	10-20yrs.	N.A.	N.A.	N.A.	N.A.
Arthritis	14,076	16,273	13,921	18,000	N.A.	xxx	4,000,000	N.A.	N.A.
Cooley's anemia	1,105	1,158	1,208	50	20-30yrs.	N.A.	100,000	N.A.	N.A.
Diabetes	11,132	15,070	13,024	4,500	N.A.	N.A.	2,000,000	N.A.	N.A.
Digestive diseases	19,888	23,628	18,836	13,000	N.A.	N.A.	16,500,000	N.A.	N.A.
Kidney disease	18,852	21,187	17,592	8,000	N.A.	N.A.	N.A.	N.A.	3/
(Artificial kidney)	(3,686)	(4,670)	(4,000)	N.A.	N.A.	N.A.	N.A.	N.A.	3/
Nutrition	8,616	9,577	8,276	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Psoriasis	460	1,118	1,000	4,000	N.A.	N.A.	1,000,000	N.A.	N.A.

NOTE: xxx - Not applicable; N.A. - Not available and cannot be estimated.

Appropriation/Program	1974 Actual Obligations (1)	1975 Estimated Obligations (2)	1976 Budget Request (3)	No. of People Afflicted (4)	Life Expectancy of Afflicted (5)	Years of Life Lost Due to Disease (6)	Loss to Economy (7) GNP	Loss to Economy (7) Fed. Taxes	Dollar Burden on Public Agencies (8)
National Institute of Neurological and Communicative Disorders and Stroke									
Stroke	$8,086	$10,910	$8,805	2,000	62 yrs.	10	$4,000,000	N.A.	N.A.
Epilepsy	5,610	6,505	5,115	2,000	xxx	xxx	2,000,000	N.A.	N.A.
Infectious disorders of the nervous system	5,008	5,670	4,870	N.A.	xxx	xxx	xxx	xxx	N.A.
Parkinsonism	4,138	4,956	3,404	200	62 yrs.	10	400,000	N.A.	N.A.
Trauma, spinal cord and head injury	6,309	10,550	6,746	1,725	xxx	xxx	4,000,000	N.A.	N.A.
(Regeneration)	(1,097)	(2,005)	(1,202)	xxx	xxx	xxx	xxx	xxx	xxx
Communicative disorders	12,164	13,760	12,359	23,500	xxx	xxx	800,000	N.A.	N.A.
Multiple sclerosis	4,770	6,967	5,903	260	52 yrs.	20	1,000,000	N.A.	N.A.
Cerebral palsy	12,890	15,390	13,197	750	52 yrs.	20	1,600,000	N.A.	N.A.
(Collaborative perinatal project)	(3,152)	(3,140)	(2,150)	N.A.	xxx	xxx	xxx	xxx	xxx
Muscular dystrophy	6,722	8,010	6,937	200	xxx	xxx	400,000	N.A.	N.A.
Tay sachs	1,347	1,500	1,373	0.25	3-4yrs.	68	13,750	N.A.	N.A.
National Institute of Allergy and Infectious Diseases									
Asthma and allergic disease centers	3,795	3,099	3,875	35,277	N.A.	N.A.	378,951[4]	N.A.	N.A.
Hepatitis	2,286	1,836	2,150	600	N.A.	N.A.	N.A.	N.A.	N.A.
Influenza and other respiratory infections	3,650	3,354	4,485	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Venereal diseases	2,937	3,259	3,020	8,500[5]	N.A.	N.A.	N.A.	N.A.	[6]
National Institute of General Medical Sciences									
Automated clinical laboratories and biomedical engineering	17,693	21,600	16,481	xxx	xxx	xxx	N.A.	N.A.	N.A.
Pharmacology-toxicology	23,032	26,100	22,787	xxx	xxx	xxx	N.A.	N.A.	N.A.
Trauma	6,614	11,775	9,400	11,500	xxx	xxx	41,500,000	N.A.	N.A.
Genetics	44,285	50,900	42,483	xxx	xxx	xxx	N.A.	N.A.	N.A.
Cellular and molecular basis of disease	48,751	56,100	48,687	xxx	xxx	xxx	N.A.	N.A.	N.A.
Minority Access to Research Careers (MARC)	4,019	500	2,000	xxx	xxx	xxx	N.A.	N.A.	N.A.
Burn centers	386	1,400	2,000	xxx	xxx	xxx	N.A.	N.A.	N.A.

NOTE: xxx - Not applicable.
N.A. - Not available and cannot be estimated.

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Appropriation/Program	1974 Actual Obligations (1)	1975 Estimated Obligations (2)	1976 Budget Request (3)	No. of People Afflicted (4)	Life Expectancy of Afflicted (5)	Years of Life Lost Due to Disease (6)	Loss to Economy (7) GNP	Loss to Economy (7) Fed. Taxes	Dollar Burden on Public Agencies (8)
National Institute of Child Health and Human Development									
Aging	$15,758	$14,949	---	xxx	xxx	xxx	xxx	xxx	xxx
Growth and development	21,108	24,029	$18,747	xxx	xxx	xxx	xxx	xxx	xxx
Mental retardation	19,789	22,631	19,227	6,000	Below avg.	N.A.	$5,500,000	$1,100,000	$3,500,000
Population	44,812	50,760	41,885	xxx	xxx	xxx	xxx	xxx	xxx
Perinatal biology and infant mortality	19,062	24,411	20,609	68 7/	-0-	70	9,500,000 7/	1,900,000 7/	500,000
(Sudden infant death syndrome)	(4,684)	(5,200)	(4,700)	(10)	(-0-)	(70)	(1,400,000)	(280,000)	(74,000)
National Institute on Aging									
Aging	(15,758)	(14,949)	16,190	xxx	xxx	xxx	xxx	xxx	xxx
National Eye Institute									
Retinal and choroidal diseases	10,066	9,021	8,021	N.A.	xxx	xxx	N.A.	N.A.	N.A.
Corneal disease	5,831	6,596	5,202	N.A.	xxx	xxx	N.A.	N.A.	N.A.
Diabetic retinopathy	4,200	4,995	4,010	157	xxx	xxx	N.A.	N.A.	N.A.
Cataracts	3,060	3,445	3,189	3,013	xxx	xxx	N.A.	N.A.	N.A.
Glaucoma	4,641	5,012	4,892	797	xxx	xxx	N.A.	N.A.	N.A.
Legal blindness 8/	---	---	---	340	xxx	xxx	1,500,000	140,000	469,000
Visual impairment 8/	---	---	---	9,600	xxx	xxx	1,400,000	N.A.	N.A.
National Institute of Environmental Health Sciences									
E.H.S. centers	3,885	5,270	5,644	xxx	xxx	xxx	xxx	xxx	xxx
Environmental mutagenesis & reproductive toxicology	1,214	2,825	1,770	xxx	xxx	xxx	xxx	xxx	xxx
Etiology of environmental diseases & disorders	5,331	6,030	5,180	xxx	xxx	xxx	xxx	xxx	xxx
Environmental pharmacology and toxicology	6,111	7,965	5,540	xxx	xxx	xxx	xxx	xxx	xxx
Environmental pathogenesis	1,884	1,736	998	xxx	xxx	xxx	xxx	xxx	xxx
Vinyl chloride	(146)	(340)	(420)	xxx	xxx	xxx	xxx	xxx	xxx
Asbestos	(547)	(1,698)	(595)	xxx	xxx	xxx	xxx	xxx	xxx
Sulfur oxide	(660)	(790)	(950)	xxx	xxx	xxx	xxx	xxx	xxx
Red tide	(9)	(24)	(28)	xxx	xxx	xxx	xxx	xxx	xxx

NOTE: xxx - Not applicable.
N.A. - Not available and cannot be estimated.

Appropriation/Program	1974 Actual Obligations (1)	1975 Estimated Obligations (2)	1976 Budget Request (3)	No. of People Afflicted (4)	Life Expectancy of Afflicted (5)	Years of Life Lost Due to Disease (6)	Loss to Economy (7) GNP	Loss to Economy (7) Fed. Taxes	Dollar Burden on Public Agencies (8)
Research Resources									
Clinical research	$41,513	$42,622	$41,601	xxx	xxx	xxx	xxx	xxx	xxx
Biotechnology research	12,569	12,154	11,430	xxx	xxx	xxx	xxx	xxx	xxx
Laboratory animal sciences and primate research	18,048	18,555	16,993	xxx	xxx	xxx	xxx	xxx	xxx
Minority biomedical support	7,048	7,264	7,165	xxx	xxx	xxx	xxx	xxx	xxx
TOTAL	1,000,541	1,189,733	1,031,030						

NOTE: xxx - Not applicable.
N.A. - Not available and cannot be estimated.
The 1974 Actual and 1975 Estimated Obligations exclude obligations from the release of the impounded funds.

1/ The NCI Programs of Special Concern are not disease oriented programs and statistics are not available nor can they be estimated for the individual programs. The latest data available estimates that 1,300,000 persons are under treatment for cancer, and the estimated person-days of disability (1972) was 88,000,000 with restricted activity and 50,000,000 sick in bed. The estimated total economic costs including direct expenditure, indirect cost of morbidity and present value of life-time earnings amounted to approximately $19,000,000,000.

2/ Contained in this figure are 1,700,000 who have acute myocardial infarction, the balance represents those afflicted with phlebitis, thrombophlebitis, hepatitis, and pulmonary embolism.

3/ It is estimated that the cost to the Social Security Administration for Artificial Kidney treatment will rise from an estimated $300 million in 1975 to $1 billion in 1980 as patients increase from 16,000 to 60,000.

4/ Asthma and hay fever only estimated for 1969.

5/ These figures include those of gonorrhea, syphilis, herpes, trichomonas and non-gonococcal urethritis.

6/ 40,000,000 hospitalization of a syphilitic insane; 5,000,000 aid to syphilitic blind.

7/ This refers to infant deaths in 1971. The figure includes 10,000 sudden infant deaths and 20,000 deaths from respiratory distress. Not included are the 55,000 fetal deaths (stillbirths) reported annually and the millions of individuals with mental retardation, epilepsy, and cerebral palsy whose disorders stem from complications of pregnancy and the birth process.

8/ Not a program area. All NEI research relates to visual disorders. This category is added to reflect economic impact only.

Mr. NATCHER. Doctor, if the figure that was submitted to me is correct, I am amazed. Millions of people, not 50 million, considerably more than 50 million. Is that your recollection?

Dr. LAMONT-HAVERS. The one great thing, of course, about the report is the fact that it doesn't necessarily count everybody once. An individual may have more than one condition.

Mr. NATCHER. Yes.

Dr. LAMONT-HAVERS. And also, as far I can remember, there was no indication, for in some of the conditions at least, or estimate of the seriousness of the particular case reported. These figures were based largely I think, some of them at least, on what individuals said they incurred—from the national health, statistics, primarily. There was a large number of individuals. There is no doubt about that.

Mr. NATCHER. Oh, yes, considerably over 50 million.

Doctor, in submitting this for the record I want you to be as concise as you can as to the number. I don't want it where there are more diseases, that is, one individual with three or four diseases. I would like to know the figure as to the number of people in this country—if it is 55 million, I would like to have that figure in that report as submitted—that have either deadly or serious diseases about which they can do little or nothing. If you would please, I would like to have that.

Dr. LAMONT-HAVERS. We will do our very best, sir.

Mr. NATCHER. Thank you very much.

REPORT ON DRINKING WATER SYSTEMS

Mr. OBEY. Dr. Rall, CBS News this morning carried a partial description of the EPA report to be released this afternoon on drinking-water systems in the country. Could you supply for the record the number of agents about which there has been some concern expressed and which have been found in drinking-water systems and the number which have received any significant degree of testing.

Dr. RALL. Yes; we will get that information and get it in the record.

[The information follows:]

NIEHS was not able to obtain a copy of the EPA report on suspect carcinogens in water supplies until April 21. This report contains a series of lists of compounds found in the water tested. It appears that 187 individual compounds are found in finished drinking water. The concentrations of all of these chemicals fortunately appears to be low.

A number of them are known potent carcinogens, including representatives of the halo ether series which I have discussed with this Committee over the last 2 years. Last year we mentioned that this compound had been found in water. In February of 1974 at a meeting at New York University NCI and NIEHS scientists informed EPA staff of the significance of this finding.

In the time available, it is impossible to review the available toxicological studies on these chemicals. We shall supply to the committee an analysis of the potential toxicologic effect of these compounds, including those compounds which have had inadequate toxicological investigation. It would seem however, that a large fraction of these agents have not been adequately studied.

Mr. OBEY. Dr. Rall, as I remember, you mentioned that the NIEHS is housed in temporary facilities.

Dr. RALL. Yes, sir. That is the majority of facilities are brick structures which we rent for our interim use until our permanent facilities are constructed.

Mr. OBEY. In other words, while most of the structures themselves are permanent—the NIEHS is renting them?

Dr. RALL. Yes; we are renting these facilities.

Mr. OBEY. What rent are you paying for those facilities?

Dr. RALL. The annual rental cost for these facilities is approximately $650,000.

Mr. OBEY. Are they located on the so-called permanent site?

Dr. RALL. No, sir; they are located on land owned by the Research Triangle Foundation adjacent to the permanent site.

Mr. OBEY. That site belongs to the Federal Government?

Dr. RALL. The permanent site is owned by the Federal Government; however, title to this land is contingent upon the construction of Federal facilities in the near future.

Mr. OBEY. Do you know what the value of the land is?

Dr. RALL. The land is valued at approximately $4 million.

Mr. OBEY. You have previously told us that you have your permanent facilities under design. What is the current status?

Dr. RALL. The first stage of the proposed permanent facility is under design and the plans are due to be completed by December 1975. It will include design for program and support facilities.

Mr. OBEY. How large will these facilities be? And about what will they cost?

Dr. RALL. The estimated gross square footage of these facilities is 432,743. The cost will be approximately $62 million.

Mr. OBEY. About how many people will they house?

Dr. RALL. The facilities will house approximately 800 people.

Mr. OBEY. How many do you have now?

Dr. RALL. The Institute currently has approximately 380 employees. This includes permanent full-time, part-time, temporary and scientists from other Institutes working collaboratively with NIEHS scientists.

Mr. OBEY. Isn't that a lot of additional space and staff?

Dr. RALL. It sounds like a lot of additional space and staff, but when one considers how much needs to be done in the area of environmental health—and how broad the range of environmental health problems are—the figures do not appear to be out of range. To be effective, we need to expand our current programs and initiate new ones that would add substantially to our knowledge in the field of environmental health research.

Mr. OBEY. Dr. Rall, what will you be able to accomplish in the new facilities that you cannot accomplish in your current facilities?

Dr. RALL. The nature of our research frequently requires us to handle hazardous compounds, as for example in our biophysics and mutagenesis programs. So we need specialized facilities to permit our laboratory personnel to handle these substances without risk.

In addition, we currently lack the facilities in which to house additional personnel with special expertise in areas we need to expand or initiate. Areas we must expand include our programs in developing short-term tests for mutagenicity, and presumptive tests for carcinogenicity; in developing methods for teratogenicity testing; in understanding the mechanisms of action of toxic substances—such as chronic and acute studies in aerotoxicology, pharmacokinetics, and biophysics; and in developing better methods for extrapolating research findings to man himself.

New areas in which we need to develop programs include chronic disease epidemiology, behavioral toxicology, and programs to develop other methods of safety testing for possible hazardous compounds. Finally, with additional space, we would be able to expand our core program to its fullest so that we could respond to problems immediately—as we could when the energy crisis developed—and predict potential problems so we would not have to wait for adverse health effects to become apparent before anything is done.

Mr. OBEY. Quite frankly, can you envision any long-term solution to your space problem other than building?

Dr. RALL. No sir. We have over the years investigated a number of alternatives to our space problems and we feel that it is in the best interest of the Government in terms of its investment in this Institute to erect this permanent facility.

Mr. OBEY. Thank you. That is all I have.

Mr. FLOOD. Mr. Michel?

ENVIRONMENTAL HEALTH RESEARCH

Mr. MICHEL. Dr. Rall, how many Federal agencies do we now have involved in environmental health research?

Dr. RALL. In 1972, the Office of Science and Technology and the Council on Environmental Quality undertook a study on the activities in the field of environmental health research. A survey was taken to identify Federal programs involved in environmental health research. As a result of this study, it was found that six agencies have significant involvement in environmental health research. There are also other agencies who have a more limited interest in the environmental health research field.

Mr. MICHEL. Can you give us some kind of an estimate of the total number of dollars being spent governmentwide?

Dr. RALL. As a result of this study, it was found that approximately $215 million annually was spent on environmental health research.

INFORMATION EXCHANGE BETWEEN AGENCIES

Mr. MICHEL. How is information exchanged between the various agencies in terms of the day-to-day progress. That is, once the planning of the grants is completed and the money is given out, how does one of your grantees keep informed with discoveries or solutions found in one of the other agencies outside NIH, such as EPA or the Atomic Energy Commission?

Dr. RALL. There are a wide variety of mechanisms available to insure effective interagency communication, cooperation, and collaboration. These range from formal coordinating groups such as the DHEW committee to coordinate toxicology and related programs, less formal

interagency groups designed to bring together scientists working in the same field such as the Interagency Panel on Environmental Mutagenesis, and widespread one-to-one contact between scientists. In the extramural area, many of these same mechanisms are used but the principal ones are undoubtedly attendant at scientific meetings, attendance at sharply focused topical conferences of the kind we support, informal and formal communication with other scientists working in the same field, and constant review of the relevant scientific literature.

COMPLETED GRANTS

Mr. MICHEL. In your justification, you say that 50 noncompeting regular research grants were completed in 1975 or that will be converted to competing status in 1976. How many of these are actually completed?

Dr. RALL. At this point, we do not know how many of these grantees will be requesting continuing support. Requests will be coming in during the next 12 months, and we anticipate that the number will be somewhat less than 50.

Mr. MICHEL. Regarding these 50 grants, could you summarize the areas of concern covered by these grants? What did we learn from the completed ones?

Dr. RALL. The areas of concern covered by these grants are in all of our program activities with the greatest numbers in the etiology of environmental diseases and disorders, and environmental pharmacology and toxicology programs. The work carried out on these grants will permit us to understand better the way in which environmental agents affect man's health.

TRAVEL

Mr. MICHEL. I note that you have an increase in your travel and transportation of persons budget. What exactly is involved here? How necessary is it for you to spend $350,000 on travel?

Dr. RALL. The travel for the Institute consists of travel in connection with research activities, site visits for grant applications, attendance at various conferences and symposiums, training of Institute staff, liaison and coordination with other agencies, and travel of my staff and myself between the Research Triangle Park, N.C., and Washington, D.C. in the conduct of official business. I believe this amount for travel is essential if we are to provide expertise, participation, and coordination in environmental health programs.

LIAISON AND INFORMING THE PUBLIC

Mr. MICHEL. In response to an item in the 1975 Senate report regarding liaison efforts as well as informing the public of the nature and results of studies, you list several steps you have taken—page 187 of justification—

You say you have been "sponsoring meetings on current problems in environmental health." Exactly what kind of meetings are those, who attends and what is done with the information obtained at those meetings?

The professional journal you publish, Environmental Health Perspectives, how is it disseminated and to whom? Would the public have access to this?

You say you also communicate with the public by informing the press. What kinds of information would you deem important to give the press and how do you assess the results you have had through this method?

Dr. RALL. Over the past 2 years the Institute has supported 15 conferences totally or in cooperation with other agencies. These conferences have been convened frequently on short notice, to bring together those concerned with specific newly emerging environmental health problems. Among the topics discussed have been asbestos, heavy metals in the environment, low-level lead toxicity, vinyl chloride-polyvinyl chloride, and marine biomedical research. We believe these meetings to be invaluable as they provide a neutral ground for regulatory agencies, regulated industry, scientists (both governmental and academic), representatives of public interest groups, and science writers to meet and hear a comprehensive review of the latest information on current and specific scientific problems. They have been extremely successful in providing a balanced perspective on current environmental problems and increasing collaboration among those concerned with environmental health research. The published proceedings of these conferences are widely distributed. In general they are published in the Institute journal, Environmental Health Perspectives.

Environmental Health Perspectives is published by the Government Printing Office and is sold on a subscription basis to anyone who orders it. The current subscription list includes professional and trade associations, other Government agencies, hospitals, individuals, industry, libraries, other research institutions State and local agencies and universities. In addition we distribute copies to NIH components, agencies with which we carry out close liaison, and science writers with interest in the area of the environment and environmental health.

I believe very strongly that enlightened public action in the field of environmental health is almost totally dependent upon an informed press. Thus, I can think of almost no situation in which the public interest would be well-served by not communicating with the press. Our efforts are aimed at providing the science reporters with a broad background into current and projected environmental problems. We do this through inviting them to participate in our working conferences, sending them copies of Environmental Health Perspectives, sending them press releases covering Institute research findings, and communicating with them informally on topics of broad interest. In addition, my senior scientists are available to the science writers to discuss their work and to serve as resource people in areas of their scientific competence. It is almost impossible to develop objective data with regard to the effectiveness of our efforts in this area. It is my belief that both the quality and quantity of the reporting of environmental health problems has increased greatly over the past several years. Also, my impression is that more and more Americans are learning that a central scientific concern and public policy issue is the effect of the environment upon man's health.

INTERNATIONAL COOPERATION

Mr. MICHEL. Since environmental problems are dependent in many aspects on international cooperation and problems, what kinds of

programs are you currently conducting to work with foreign government programs? What other countries have environmental health research programs?

Dr. RALL. We have a wide variety of international activities ranging from formal cooperation with other countries to collaboration between our scientists and scientists working in laboratories abroad, and then we have extensive international collaboration ongoing under the aegis of the World Health Organization. In the area of formal intergovernmental cooperation, we have responsibility for the environmental panel of the United States-Japan cooperative medical science program, and carry major responsibility for two U.S.-U.S.S.R. agreements: The Health Agreement, and the Environmental Protection Agreement.

MANAGEMENT OF GRANT PROGRAMS

Mr. MICHEL. Of the 38 positions allotted for research management and program services, how many will be involved in the surveillance over approximately 200 grants during this year?

Dr. RALL. Of the 38 positions allotted for research management and program services, 12 are allotted to scientific and administrative management of our grants program. This surveillance includes the review and evaluation of research, fellowships, and training grant applications for presentation to the Institute's advisory committee; monitoring of ongoing grants; and liaison with applicants, grantees, advisory bodies, other components of the National Institutes of Health and the Department of Health, Education, and Welfare, and other interested organizations.

HEALTH EFFECTS OF ENERGY

Mr. CONTE. Dr. Rall, your justification states that you are prepared to give us a status report on developments in the health effects of various alternatives. Would you summarize for me, and elaborate for the record, on your progress to date in investigating these health hazards, and what new areas you intend to get into during the coming year?

Dr. RALL. This activity grew out of the administration's efforts to develop energy self-sufficiency for the United States. We have been involved in this planning effort for the last year and will soon be beginning research under an interagency agreement with the Environmental Protection Agency. At this point, with the committee's permission, I would like to insert a staff paper which describes the current status of this effort.

(The material referred to appears beginning at page 1061a.)

The President's budget does not provide for developing new areas of research.

OBLIGATION OF RESCISSION FUNDS

Mr. CONTE. The administration sent up a $6.9 million rescission for your Institute, which we rejected. Will that money all be obligated this year?

Dr. RALL. Yes. Based on information that we have available for grants and contracts, the Institute will have no difficulty in obligating all of its funds.

ENERGY-RELATED HEALTH EFFECTS RESEARCH:

THE KING/MUIR REPORT AND NIEHS

As part of the nation's massive effort to increase its supply of energy, the Administration's budget for FY 1975 requested an increase of $134 million for the support of research into the potential adverse health and environmental side effects of the various energy technologies under development. The President's budget allotted the requested increase to EPA pending recommendations from an interagency task force on the distribution of these funds between EPA and other agencies for pursuit of the highest priority research objectives.* From April until September, 1974, the task force met frequently to identify research needs, assign priorities, and contend for declining funds (Congressional action reduced the increase to $78 million**) which were finally allocated among five research categories as follows:

	FY 1975 increases $ in millions
Health Effects	20.0
Ecological Effects	23.2
Measurement and Monitoring	13.4
Environmental Transport	10.3
Assessment	11.2***
	78.1

The distribution among agencies is indicated in Tab A from the interagency report.

HEW dissented from the allocations recommended in the report on the grounds that high priority health research needs were not being met by the proposed distribution.

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*The task force was composed of representatives from AEC, EPA, NSF, FEA, TVA, and the Departments of HEW, Agriculture, Commerce, and Interior, working under the overall chairmanship of Drs. Don King, State, and Warren Muir, CEQ.

**The appropriations subcommittees handling the EPA budget in FY 1975 were, on the House side, Agriculture-Environmental and Consumer Protection (Jamie Whitten, Chairman) and, on Senate side, the Agriculture, Environmental and Consumer Protection (John McClellan, Chairman).

***EPA may reduce Assessment by $2M in allocating a final round of Congressional reductions to bring the total increase appropriated in FY 1975 to $76M.

The report of the interagency group proposed that NIEHS undertake energy-related health effects research amounting to $3,420,000 and ecological (marine biological) effects research amounting to $205,000. The specific tasks assigned to NIEHS, and the associated dollar amounts are outlined in Tab B. NIEHS advertised in the NIH Guide last November for research grant applications in the areas assigned to the Institute (not including marine ecological research).

The President's Budget for FY 1976 intends that at least the same amount will be available to the agencies identified in the report -- again by transfer from EPA -- for continuation of the programs initiated in FY 1975.

Although the King/Muir report recommended additional positions to support the research, no positions have been made available for this purpose.

Staff of NIEHS and EPA are presently working out the details of an interagency agreement for the transfer of funds and of the proposed research.

SUMMARY OF ALLOCATIONS BY PERFORMING AGENCY FOR FY 1975
(In Thousands)

TAB A

Table 1.b.

AGENCY	CATEGORIES					
	Pollutant Characterization, Measurement and Monitoring	Environmental Transport Processes	Health Effects	Ecological Effects	Integrated Assessment	TOTAL
AEC (Direct)*	600	2600	2000	7500	3800	16500
(EPA pass)	1538	930	5978	2981	755	12182
DOI	265	60	--	2560	--	2885
EPA**	2872	3205	6466	3905	3697***	20145
NBS	1190	--	--	--	--	1190
NOAA	1200	535	--	1869	--	3604
NSF*	3105	2535	--	1382	1563	8585
TVA	320	335	--	1240	400	2295
NIOSH	390	--	2159	--	--	2549
NASA	795	--	--	--	--	795
USGS	1130	--	--	--	--	1130
USDA	--	50	--	1565	670	2285
NIEHS	--	--	3420	(HEW)205	--	3625
DOC	--	--	--	--	80	80
FPC	--	--	--	--	75	75
HUD	--	--	--	--	160	160
TOTAL	13405	10250	20023	23207	11200	78085

*NSF and AEC (direct) funds were allocated and will be expanded within these agencies.

**EPA received $53 million of which $20,145,000 would be expanded within the agency, and $32,855,000 would be passed-through to other agencies. Pass-throughs for each category are as follows: Pollutant Characterization, Measurement and Monitoring - $6,828,000; Environmental Transport Processes - $1,910,000; Health Effects - $11,557,000; Ecological Effects - $10,420,000; and Integrated Assessment - $2,140,000.

***$3 million of EPA funds are for control technology.

1061C

TAB B

ENERGY RELATED HEALTH AND

ECOLOGICAL RESEARCH ASSIGNED TO NIEHS

BY THE KING/MUIR REPORT

Health Effects

°Develop physiological indicators to estimate damage to man ($860,000).

°Determine the mechanisms of incorporation, metabolism, deposition, and turnover of hazardous agents ($350,000).

°Determine the relationships of metabolism and fate and the toxicology of particulates and organic compounds ($350,000). [responsibility for task shared with NIOSH which has separate allocation amounting to $500,000]

°Determine the dose-effect relationships for physiological effects ($600,000). [responsibility for task shared with NIOSH and AEC which have separate allocations amounting to $1,000,000]

°Determine the dose-effect relationships for mutagenic agents ($460,000). [responsibility for task shared with AEC which has separate allocation amounting to $600,000]

°Develop and test models for extrapolation of cellular and animal data to man ($400,000).

°Identify damage to cells and cell components ($400,000). [responsibility for task shared with AEC which has separte allocation amounting to $100,000]

Ecological (Marine biological) Effects

°Determine the physiological mechanisms of transport, accumulation and excretion of metals in marine organisms and mammals ($90,000).

°Determine the accumulation, distribution, metabolism and excretion of individual isomers present in crude oil and warm water species ($35,000).

°Determine the physiological effects of pre-exposure of selected warm and cold water marine species to heavy metals, other pollutants on toxicity of various hydrocarbon isomers and on the accumulation, distribution, metabolism and excretion of various hydrocarbons ($35,000).

°Determine the carcinogenic effects of petroleum hydrocarbons on selected marine and estuarine organisms ($45,000).

PERMANENT FACILITIES

Mr. CONTE. Can you give me a progress report on the construction of your laboratory facilities in North Carolina?

Dr. RALL. The first stage of the proposed permanent facilities for the Institute are under design. The design for these facilities should be completed by December 1975. The construction of the estimated 432,743 gross square feet is projected to take approximately 30 months and cost approximately $62 million. No land acquisition costs will be involved as the Government currently holds title to 509 acres of land in the Research Triangle Park, N.C. Title to this land is contingent upon the construction of Federal facilities on the land in the near future. To date, no construction funds have been appropriated.

ASBESTOS

Mr. CONTE. In your statement, you said that when Congress added $1 million to your 1975 request and directed a study of ingested asbestos, you could immediately respond. Nine months later, you are making plans to award two contracts. Would you call this an immediate response?

Dr. RALL. In response to the directive of Congress for the Institute to direct a long-term study on the effects of ingested asbestos, a draft protocol was developed in August 1974. It was our feeling that before work on this important area was implemented, the protocol should be reviewed by all of those interested in this area of research. Because it was uncertain that the appropriation would be available for obligation, we waited until February to convene a meeting to review this protocol. As a result of this meeting, a major modification was made in the protocol—four specific contract activities were planned, rather than one as in the original protocol. Also because of the expense which prospective contractors would incur in preparing contract proposals, we did not think it proper to solicit research contract proposals until it was clear that funds would be available. After congressional action on the President's proposed rescission in mid-March, requests for proposals (RFP) were issued and two research contracts will be awarded prior to June 30, 1975. The other two research contracts will be funded at a later date.

HEALTH EFFECTS OF ENVIRONMENTAL SMOKE

Mr. CONTE. A great deal has been said and written about the relationship between smoking and cancer. What kind of work has been done on the effect of environmental smoke on health—that is, the effect of being in a smoke-filled-room type of environment.

Dr. RALL. There has been some work on this problem. There are a number of factors which increase the difficulty of experimental design, for example, size of room, how well sealed is the room. There are, however, a number of problems related to the issue of indoor air pollution. For example, smoking can raise the carbon monoxide levels in the room. In addition, in the interest of energy conservation, we are attempting to increase insulation and decrease heat leakage. This results in our homes becoming more nearly airtight, and raises the potential problems of such things as increased oxides of nitrogen from

gas burning stoves and ovens. In addition, recently three scientists in England reported that for children under 1 year of age, exposure to cigarette smoke, generated when parents smoked, doubled the risk for the infant of an attack of pneumonia or bronchitis.

LETHAL EFFECTS

Mr. CONTE. There has been mention made of the effect of combinations of nonlethal amounts of toxic substances producing lethal effects. Could you tell me what sorts of combinations have been investigated? What is planned in this area for the future?

Dr. RALL. The very real problem of the lethal effects resulting from combinations of nonlethal compounds has been very well studied in the field of therapeutic drugs. Among the best known of these is the combination of barbiturates and alcohol, barbiturates and anticoagulants, and certain antidepressant drugs and ripe cheese.

Much less has been done with environmental agents. However, there are two examples in the field of air pollutants. It has been demonstrated that ozone and sulfur dioxide combines to cause pronounced lung irritation, and that sulfur dioxide greatly enhances the cancer-producing effect of benzpyrene. Multiagent effect is an important area for further research. We will continue our efforts to establish more of these kinds of relationships.

"MOUSE MODEL"

Mr. CONTE. Dr. Rall, you mentioned your mouse model of the toxic effects of DES. Could you tell me exactly what a mouse model is, and how it works? Do you have similar models for other substances?

Dr. RALL. One of the real problems in environmental health is the difficulty in making controlled observations directly on man. The long time between exposure and effect in many environmental agents make widespread research on humans impractical from time as well as ethical points of view. Thus, it is essential that appropriate animal systems be developed whose results, when combined with the results of other test systems, will forecast toxic effects in man. It is a model in the sense that it permits inducing toxic effects in animals that could not be done in a human experimentally. In the case of DES, diethylstilbestrol, scientists at NIH have discovered that the female mouse can serve as a model for the human female. That is, the young female mice develop the same sort of cancers found in young women, whose mothers were treated with DES. There are a number of experimental models being developed in this area as in other fields, some cellular, some animal, some statistical. Progress in this field is heavily dependent upon an adequate number and variety of dependable models.

TESTING OF HAZARDOUS SUBSTANCES

Mr. CONTE. Do you have operable short-term tests for screening chemicals and consumer products? Are they effective for all types of substances? Which ones?

Dr. RALL. Yes; we do. While these tests are generally effective in screening chemicals and constituents of consumer products, they are

not effective for all types of effects. Thus, the development of tests which can screen for additional effects are critically needed.

Mr. CONTE. Are you now able to establish priorities based on the projected public health hazard of untested chemicals. What would you consider your top priorities?

Dr. RALL. No, sir, regrettably we cannot. This is a major problem facing all of us in this field. We have learned some general principles which we can apply when attempting to forecast the potential toxicity of a new compound. For example, is the compound structurally similar to a compound whose toxicity has already been established? Again, based on our experience to date, we would say that a high priority for testing should be given any compound whose use will be widespread and which will be manufactured in large quantities.

Mr. CONTE. How does the short-term test for mutagenicity work?

Dr. RALL. The genetic apparatus is very similar from bacteria to man. It is possible, therefore, to look for mutations in simple one-cell organisms such as bacteria, or yeast or in mammalian—even human—cells grown in tissue culture. A genetic change—a possible mutation is identified—such as a change in color or growth requirements. The normal rate of occurrence of this change is determined.

To test for mutagenicity, a chemical is added to the nutrient medium for the cells, the culture is incubated, then the change—a red color in normally colorless cells, for example, is looked for. Since many compounds must be chemically altered or metabolized by the enzymes in the body to become active, that is, toxic or mutagenic, often an enzyme preparation from rodent liver, lung, et cetera is added to the cell—nutrient medium—chemical mixture. Such tests can be performed in as little as a few days and cost one to two thousand dollars.

NIEHS-NIOSH RELATIONSHIPS

Mr. CONTE. How does your work relate to that carried on by the National Institute of Occupational Safety and Health? Do you complement each other or duplicate? Where do you draw the line between your Institute in terms of jurisdiction over some of these environmental health problems like PCV's?

Dr. RALL. In general, our work ranges across the entire area of the environment with particular emphasis on those chemical, physical, and biological factors in the environment which can have an adverse effect upon man's health. Our interest in the workplace rises out of the knowledge that there is increasing evidence that occupational exposures frequently are the precursors of a general environmental problem, such as families of asbestos workers developing asbestosis. The National Institute for Occupational Safety and Health has very broad responsibilities in the field of occupational safety and health which go far beyond our specific areas of interest. For example, they have responsibility for employee general health, safety programs, et cetera. The work of our two Institutes is conducted in a coordinated, collaborative way. The Director of the National Institute for Occupational Safety and Health or his representative sits on the Toxicology Coordinating Committee. In addition, Dr. John Finklea, the new Director of NIOSH, and I have been professional associates for 4 years. As a result, he and I are able to discuss our mutual and complimentary problems informally and effectively. In an area like polyvinyl

chloride, NIOSH primarily concerns itself with the hazard which the compound may constitute for the worker and we look at its general environmental effects. When a conference on this subject was held a year ago, NIOSH and our Institute collaborated in its support, together with a wide range of non-Federal organizations.

MULTIYEAR AWARDS

Mr. CONTE. How many multiyear awards do you plan to make this year. For how much?

Dr. RALL. We have no plans to multiyear award any grants during 1975.

AVERAGE GRANT AWARD

Mr. CONTE. What is your average grant award this year? How does it compare to previous years? What accounts for the difference, if any?

Dr. RALL. The average grant award this year is $66,000, as compared to $74,000 in 1974, and $64,000 in 1973. Several large multiyear funding awards early in 1974 resulted in a higher average for that year.

UNFUNDED GRANTS

Mr. CONTE. How many approved grants will be unfunded this year?

Dr. RALL. The Institute will not be able to fund 75 approved grants in 1975 and the estimate for 1976 is 172.

ENERGY

Mr. CONTE. You have about a $3.8 million decrease in your budget from last year. Will you be able to conduct this increasingly important energy-related research with less money?

Dr. RALL. Mr. Conte, as is indicated in the staff paper I submitted in answer to your earlier question, the majority of the funding for our energy-related research will come by transfer from EPA. As you know, the President has announced that work in the energy field will receive the highest priority. Thus, we anticipate being able to continue our efforts to develop research into the health effects of the energy crisis.

NEW CENTER

Mr. CONTE. Your justification states that you will be adding a new university-based research center in 1975. Have you done this yet? Where is the center? What does/will it do?

Dr. RALL. We are in the process of adding a new center in 1975. It will be located at the University of Rochester in New York. The center will have outstanding expertise and research capabilities in chemistry and hazards of mercurials and other heavy metals. During the coming years, we expect this center to contribute significantly to the objectives of our Institute.

DISSEMINATION OF RESULTS

Mr. CONTE. Would you elaborate on the specific ways in which you disseminate the results of your research to the medical community and the health care delivery system?

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Dr. RALL. The majority of our research relates to the regulatory agencies and to industry. The Institute has a wide range of activities aimed at insuring that its research is incorporated into regulatory practice. Some of our research, which is grant supported, has a direct bearing on primary medical care. In those instances, we publish our results in the journals typically read by doctors in practice, for example, "Journal of the American Medical Association" and the "New England Journal of Medicine."

Another activity in which we communicate with physicians is our alert practitioners program. This is a collaborative effort with the American Academy of Pediatrics, and it provides an avenue for two-way communications between our Institute and physicians. This program involves medical students who serve as interviewers and obtain environmental exposure histories from patients in an effort to help uncover environmental hazards. Through such histories, we hope to track down the causes of birth defects and diseases of unknown etiology that may be environmentally induced.

This program began as a demonstration project in 1972 and has been enthusiastically received by many pediatricians. Its aim is to have all pediatricians in the country report directly to the Academy any leads on environmental hazards involved in birth defects. At present, four major medical organizations are participating. Soon the program will expand its contacts to include medical schools and the AMA in an effort to broaden interests in environmental medicine.

INTRAMURAL RESEARCH

Mr. CONTE. What portion of your research is intramural? Do you foresee increases ahead?

Dr. RALL. Approximately 35 percent of our research is intramural research. The intramural program, as well as the extramural research program, provides a prime and unique focus for national and international efforts to deal with the effects of the environment on man's health. We do foresee increases in this area if we are to further validate short-term tests for use in hazard-screening programs and determine the effects of exposure to genetically active chemicals on man himself.

ENVIRONMENTAL MUTAGENESIS AND REPRODUCTIVE TOXICOLOGY

Mr. CONTE. There seems to be a significant decrease in funding for environmental mutagenesis and reproductive toxicology, from $2.8 down to $1.8 million. Why is there such a big decrease?

Dr. RALL. Congress' action on the President's proposed rescission resulted in increased amounts being made available for environmental mutagenesis and reproductive toxicology in 1975. This resulted in a decrease of approximately $1 million for this program between 1975 and 1976.

FREONS AND FLEUROCARBONS

Mr. CONTE. What sort of research is being conducted on freon and fleurocarbons in general? Do you know what the long-term effects of these substances may be?

Dr. RALL. There are two principle health effects from freon and fleurocarbons. The first is that of direct cardio-toxicity. That is a problem only these compounds are misused or used under extremely unusual conditions. The second is the possibility that they can destroy the ozone layer which protects the earth from ultra-violet light. Dr. Frederick Urbach of the Skin and Cancer Hospital in Philadelphia is trying to relate the amount of ultraviolet radiation received at ground level with the incidence of skin cancer. The NIEHS has provided almost all the support for the biological research conducted in this area. Although the ozone effect is not yet proven, it appears to me to be quite likely.

EXTRAMURAL STAFF

Mr. CONTE. How many staff people do you have watching over your 200 grants? Is this number necessary and/or adequate?

Dr. RALL. The Institute has 12 people responsible for program and administrative management of our grants program. This number of people is necessary and for the past several years, we have been staffed at an absolute minimal level, even though workload has increased. I feel that effective programing would require additional staffing in this area.

Mr. CONTE. Thank you.

Mr. FLOOD. That concludes this hearing. Thank you, gentlemen.

Dr. RALL. Thank you, sir.

Justification of the Budget Estimates

Appropriation Estimate

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

To carry out, except as otherwise provided, sections 301 and 311 and Title IV, Part I of the Public Health Service Act, with respect to environmental health sciences, [$34,949,000] *$31,113,000.*

For the "National Institute of Environmental Health Sciences" for the period July 1, 1976, through September 30, 1976, $7,760,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation

	1975[1/] Revised	1976 Estimate
Appropriation.....	$34,949,000	$31,113,000
Comparative transfers to:		
"Office of the Director, NIH" (To transfer Institutional Relations Branch from Division of Research Grants, NIH Management Fund).....	-6,000	---
"Research Resources" (For the funding of the rhesus monkey supply program).....	-6,000	---
Total obligations.....	34,937,000	31,113,000

[1/] Excludes 1973 appropriation restorations in the amount of $844,000

Summary of Changes

1975 Estimated obligations	$34,937,000
1976 Estimated obligations	31,113,000
Net change	-3,824,000

	1975 Pos.	1975 Amount	Change from 1975 Pos.	Change from 1975 Amount
Increases:				
A. Built-in:				
1. Within-grade pay increase..	---	---	---	+$35,000
2. One additional day of pay in 1976.....	---	---	---	+16,000
3. Wage board pay increase....	---	---	---	+12,000
4. Annualization of 1975 pay raise in 1976.....	---	---	---	+75,000
5. BEC rate increase.....	---	---	---	+2,000
6. Utility increase.....	---	---	---	+35,000
7. Postage increase.....	---	---	---	+2,000
Subtotal.....	---	---	---	+177,000
B. Program:				
1. Research grants:				
a. Noncompeting continuations.....	---	$7,385,000	---	+6,915,000
b. Competing.....	---	---	---	+1,285,000
c. Special programs.....	---	5,543,000	---	+479,000
2. Fellowships:				
a. Noncompeting continuations.....	---	205,000	---	+934,000
3. Intramural laboratory and clinical research.....	202	8,932,000	-2	+710,000
Subtotal.....	---	---	-2	+10,323,000
Total increases.....	---	---	-2	+10,500,000
Decreases:				
A. Built-in:				
1. Payment to "National Institutes of Health Management Fund" for centrally furnished services.....	---	851,000	---	-17,000
B. Program:				
1. Research grants:				
a. Noncompeting completed, converted, or terminated.....	---	---	---	-5,900,000
b. Competing completed or converted to noncompeting.....	---	---	---	-4,674,000
c. Special programs:				
(1) Noncompeting completed or terminated..	---	---	---	-99,000
(2) Competing completed or converted to noncompeting	---	---	---	-96,000

	1975 Pos.	1975 Amount	Change from 1975 Pos.	Change from 1975 Amount
2. Fellowships:				
a. Noncompeting completed or terminated.....	---	---	---	-$847,000
b. Competing completed or converted to noncompeting.....	---	---	---	-855,000
3. Training grants:				
a. Noncompeting completed or converted to competing status...	---	2,215,000	---	-762,000
4. Research and development contracts.....	---	2,949,000	---	-1,074,000
Subtotal.....	---	---	---	-14,307,000
Total, decreases.....	---	---	---	-14,324,000
Total net change.....	---	---	-2	-3,824,000

Explanation of Changes

Increases:

A. Built-in: The increases will provide: 1. $35,000 for within-grade pay increases in 1976 -- $30,000 for Intramural Laboratory and Clinical Research and $5,000 for Research Management and Program Services; 2. $16,000 for one additional day of pay in 1976 -- $14,000 for Intramural Laboratory and Clinical Research and $2,000 for Research Management and Program Services; 3. $12,000 for the Wage Board pay increase for Intramural Laboratory and Clinical Research; 4. $75,000 for annualization of 1975 pay raise costs in 1976 -- $68,000 for Intramural Laboratory and Clinical Research and $7,000 for Research Management and Program Services; 5. $2,000 for increase in Bureau of Employee Compensation (BEC) for Intramural Laboratory and Clinical Research; 6. $35,000 for utility increase for Intramural Laboratory and Clinical Research; and 7. $2,000 for postage increase for Intramural Laboratory and Clinical Research.

B. Program:

1. Research grants:

a. The increase of $6,915,000 represents the continuation costs of 63 competing awards made in 1975 ($4,674,000); 21 competing awards made in 1975 from the 1973 appropriation restorations ($844,000); and 2 competing multiyear awards made in 1974 ($1,397,000).

b. The increase of $1,285,000 in competing research grants represents 13 competing continuations.

c. The increase of $479,000 will provide for increased continuation costs of 7 currently active centers ($374,000); continuation costs of 4 new Research Career Development Awards made in 1975 ($100,000); and an increased assessment for Scientific Evaluation ($5,000).

2. Fellowships:

a. The increase of $934,000 provides for continuation costs of 16 competing individual awards made in both 1974 and 1975 ($234,000), and continuation costs of 7 institutional awards made in 1975 ($700,000).

3. Intramural laboratory and clinical research: The increase of $710,000 would permit the expansion of our intramural research program, particularly in the area of environmental mutagenesis and reproductive toxicology.

Decreases:

A. Built-in: The decrease of $17,000 is for a reduced assessment for the NIH Management Fund for centrally furnished services.

B. Program:

1. Research grants:

a. The decrease of $5,900,000 represents 50 noncompeting regular research grants that were completed in 1975 or that will be converted to competing status in 1976 ($2,215,000) and 51 lower priority noncompeting grants ($3,685,000) which will not be funded in 1976.

b. The decrease of $4,674,000 reflects 63 competing grants from 1975 converted to noncompeting status.

c. Special programs:

(1) The decrease of $99,000 represents 1 noncompeting Research Career Development Award completed in 1975 ($24,000) and 3 lower priority noncompeting Research Career Development Awards ($75,000) which will not be funded in 1976.

(2) The decrease of $96,000 reflects 4 competing Research Career Development Awards from 1975 converted to noncompeting status in 1976.

2. Fellowships:

a. The decrease of $847,000 represents 10 individual noncompeting awards completed in 1975 ($147,000) and 7 lower priority noncompeting institutional awards ($700,000) which will not be funded in 1976.

b. The decrease of $855,000 reflects 11 individual awards and 7 institutional awards from 1975 converted to noncompeting status in 1976.

3. Training grants:

a. The decrease of $762,000 reflects the completion of 7 noncompeting training grants in 1975.

4. Research and development contracts: The decrease of $1,074,000 represents 5 research contracts which will not be funded in 1976.

Obligations by Activity

Page Ref.		1975 Base Pos.	1975 Base Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
196	Environmental health sciences centers ..	---	$5,270,000	---	$5,644,000	---	+$374,000
197	Environmental mutagenesis and reproductive toxicology	---	2,825,000	---	1,770,000	---	-1,055,000
199	Etiology of environmental diseases and disorders.....	---	6,030,000	---	5,180,000	---	-850,000
202	Environmental pharmacology and toxicology.....	---	7,965,000	---	5,540,000	---	-2,425,000
204	Environmental pathogenesis.....	---	1,736,000	---	998,000	---	-738,000
206	Intramural laboratory and clinical research.....	202	9,603,000	200	10,464,000	-2	+861,000
208	Research management and program services.....	38	1,508,000	38	1,517,000	---	+9,000
Total obligations		240	34,937,000	238	31,113,000	-2	-3,824,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	240	238	-2
Full-time equivalent of all other positions	100	107	+7
Average number of all employees	334	341	+7
Personnel compensation:			
Permanent positions	$3,792,000	$3,898,000	+$106,000
Positions other than permanent	776,000	855,000	+79,000
Other personnel compensation	105,000	115,000	+10,000
Subtotal, personnel compensation	4,673,000	4,868,000	+195,000
Personnel benefits	487,000	516,000	+29,000
Travel and transportation of persons	332,000	350,000	+18,000
Transportation of things	30,000	32,000	+2,000
Rent, communications and utilities	1,050,000	1,085,000	+35,000
Printing and reproduction	60,000	65,000	+5,000
Other services	1,688,000	1,991,000	+303,000
Project contracts	2,949,000	1,875,000	-1,074,000
Payment to NIH Management Fund	851,000	834,000	-17,000
Supplies and materials	1,340,000	1,540,000	+200,000
Equipment	600,000	700,000	+100,000
Grants, subsides and contributions	20,877,000	17,257,000	-3,620,000
Total obligations by object	34,937,000	31,113,000	-3,824,000

Significant Items in House and Senate
Appropriation Committee Reports

Item 1975 House Report	Action taken or to be taken
1. The Committee has included $1,000,000 in the bill to initiate the long-term study on the effects of ingested asbestos.	1. The Institute is making plans to study the hazards of ingested asbestos. Following a meeting held in early February to develop specific research protocols, the Institute developed requests for proposals for contracts in this area. It is the Institute's intention to award 2 research contracts (totaling $1,000,000) in this area prior to June 30,1975.
2. The Committee wants to emphasize that the maintenance and effective use of adequate liaison arrangements is a direct responsibility of the NIEHS because of its central role in the identification and assessment of environmental health problems.	2. The Institute has personnel primarily involved in maintaining adequate liaison between the various agencies, as well as directly with industry through technological surveillance. The Director of NIEHS serves as Chairman of the DHEW Committee to Coordinate Toxicology and Related Programs, which insures close coordination of HEW programs in this area. Individual scientists are encouraged to communicate on a scientist-to-scientist basis with those in industry and other agencies.
3. The Committee hopes that the impressive cooperative research arrangement between the Institute and the various university-based research centers which it supports can be further expanded and strengthened.	3. Since the university-based research centers focus on particularly critical problems, they are frequently called upon by the Institute for assistance and consultation regarding problems of critical and urgent national interest. Center Directors' meetings are held twice a year to discuss current research and imminent problems in the area of environmental health research. In recognition of the importance of this program, a new center is being added in 1975.

4. Which source or sources are selected for energy development will ultimately depend upon many factors, but the Committee believes that a principal factor should be the health effects associated with each energy option. A substantial part of the increase is to be used to address the problems posed by petrochemicals and new energy sources. It is the Committee's view that the National Institute of Environmental Health Sciences, as the principal Federal agency charged with the development of knowledge on the adverse effects on health resulting from environmental factors, should play a major role in the planning and conduct of health-related research in this area. The Committee will look forward to hearing a report next year on the status of this effort.	4. The NIEHS is one of a number of agencies cooperating in the development of a government-wide plan for research to determine the health effects of many energy alternatives. At the hearings, the Institute will be prepared to report on the status of the developments in this very rapidly-moving area.
1975 Senate Report	
1. As health is such an important factor in the determination of which energy choice should be made, it is vital that the NIEHS be prepared to render its best scientific advice in this area. The Committee concurs in the views of the House Committee regarding the role of the NIEHS in the planning and conduct of health research in the energy area.	1. See House Report, Item 4, above.
2. The Committee directs that the study on the health effects of emissions of sulfur oxides to the air, resulting from any conversions to burning coal, commence immediately within the funds provided by the Congress.	2. P.L. 93-319 authorizes and directs the NIEHS in cooperation with the Environmental Protection Agency to determine the health effects of emissions of sulfur oxides to the air, resulting from any conversions to burning coal, by conducting a study of chronic effects among exposed populations. Funds are not available for this study.
3. The Committee directs the Institute to begin the development of a major program in the area of marine bio-medicine and marine pharmacology within the increase provided by the Congress.	3. The NIEHS has begun to develop studies of the effect of pollutants on affected marine species in order to get "advance" information on possible human effects. A meeting was held in February 1975 to investigate possible research opportunities in this area and the current status of marine bio-medicine laboratories. In the coming months, a second meeting of this group will be held to discuss future directions for marine biomedical research.

4. The Committee will expect that a portion of the Congressional increase be used to expand research currently being done on the effects of vinyl chloride in light of the apparent link between vinyl chloride and angiosarcoma (liver cancer).	4. Research is currently being conducted on vinyl chloride and its analogs to investigate the mechanisms by which they induce liver toxicity and cancer via activated metabolic intermediates. Activated intermediates appear to be primary carcinogens in the action of some chlorinated compounds.
5. The Committee recommends that NIEHS vigorously continue its liaison efforts as well as inform the public of the nature and results of studies.	5. NIEHS is continuing to carry out its responsibility in this area by: (a) sponsoring meetings on current problems in environmental health; (b) participating in joint-planning activities; (c) publishing its professional journal, Environmental Health Perspectives; (d) conducting joint international endeavors; (e) publishing results of NIEHS scientists' work; and (f) communicating with the public by informing the press.
6. The Committee concurs with the House recommendation for a long-term study of the effects of ingested asbestos.	6. See House Report, Item 1, above.
7. The Committee directs the Institute to begin a study of the effects of the red tide on human health.	7. Research is currently underway to study the physical characterization of respiratory irritants associated with Red Tide on the west coast of Florida.

Authorizing Legislation

Legislation	1976 Authorization	1976 Appropriation Requested
Public Health Service Act Section 301--Research and Investigation, in general.....	Indefinite	
Title III, Part A--National Institute of Environmental Health Sciences...	Indefinite	$29,368,000[2/]
Title IV, Part I--National Research Service Awards.....	[1/]	1,745,000[2/]

[1/] Authorization expires June 30, 1975, extension legislation is proposed.

[2/] Funding estimate only.

National Institute of Environmental Health Sciences

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$15,933,000	$15,933,000	$15,983,000	$15,983,000
1967	24,312,000	24,298,000	24,298,000	24,298,000
1968	19,896,000	16,570,000	19,896,000	16,570,000
1969	17,548,000	16,990,000	17,548,000	17,269,000
1970	17,777,000	17,777,000	17,777,000	17,777,000
1971	19,397,000	20,067,000	21,067,000	20,067,000
1972	24,840,000	25,945,000	31,445,000	25,945,000
1973*	28,532,000	30,412,000	31,456,000	30,412,000*
1974	25,263,000	28,879,000	28,879,000	28,397,000**
1975	28,672,000	32,582,000***	34,988,000	34,937,000
1976	31,113,000			

*Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

**Appropriation after reduction

***Excludes Research and Devlopment Contracts not considered by the House due to lacking authorization.

National Institute of Environmental Health Sciences

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$15,933,000	$15,933,000	$15,983,000	$15,983,000
1967	24,312,000	24,298,000	24,298,000	24,298,000
1968	20,615,000	17,289,000	20,615,000	17,289,000
1969	18,099,000	17,541,000	18,099,000	17,820,000
1970	18,328,000	18,328,000	18,328,000	18,328,000
1971	19,843,000	20,620,000	21,620,000	20,620.000
1972	25,271,000	26,436,000	31,991,000	26,436,000
1973*	29,017,000	30,956,000	32,000,000	30,956,000*
1974	25,263,000	28,879,000	28,879,000	28,397,000**
1975	28,684,000	32,594,000***	35,000,000	34,949,000
1976	31,113,000			

*Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

**Appropriation after reduction

***Excludes Research and Development Contracts not considered by the House due to lacking authorization.

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DHEW - National Institutes of Health

CROSSWALK - 1975 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute of Environmental Health Sciences
(Dollars in thousands)

Program \ Mechanism	Research Grants				Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	TOTAL
	Regular Program		Specials							
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Environmental health sciences centers....	---	---	$5,270	---	---	---	---	---	---	$5,270
2. Environmental mutagenesis and reproductive toxicology..	$785	$1,122	---	$25	---	$113	---	$780	---	2,825
3. Etiology of environmental diseases and disorders.....	2,750	1,636	---	50	$598	92	---	904	---	6,030
4. Environmental pharmacology and toxicology.....	3,220	1,355	---	173	1,263	829	---	1,125	---	7,965
5. Environmental pathogenesis.....	630	561	---	25	354	26	---	140	---	1,736
6. Intramural laboratory and clinical research.....	---	---	---	---	---	---	$9,603	---	---	9,603
7. Research management and program services.....	---	---	---	---	---	---	---	---	$1,508	1,508
Total obligations.....	7,385	4,674	5,270	273	2,215	1,060	9,603	2,949	1,508	34,937

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1976 PRESIDENT'S BUDGET

INSTITUTE: National Institute of Environmental Health Sciences
(Dollars in thousands)

Program \ Mechanism	Research Grants						Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	TOTAL
	Regular Program		Specials		Training Programs					
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Environmental health sciences centers....	---	---	$5,644	---	---	---	---	---	---	$5,644
2. Environmental mutagenesis and reproductive toxicology..	$899	$138	---	---	---	$25	---	$708	---	1,770
3. Etiology of environmental diseases and disorders.....	3,394	618	---	$25	$162	119	---	862	---	5,180
4. Environmental pharmacology and toxicology.....	3,629	454	---	133	1,034	133	---	157	---	5,540
5. Environmental pathogenesis.....	478	75	---	25	257	15	---	148	---	998
6. Intramural laboratory and clinical research.....	---	---	---	---	---	---	$10,464	---	---	10,464
7. Research management and program services.....	---	---	---	---	---	---	---	---	$1,517	1,517
Total Obligations.....	8,400	1,285	5,644	183	1,453	292	10,464	1,875	1,517	31,113

National Institute of Environmental Health Sciences

Budget Mechanism

	1975*			1976		
	Number	FTE	Amount	Number	FTE	Amount
Grants						
Regular						
Non-competing	120	---	$7,385,000	105	---	$8,400,000
Competing	18	---	1,792,000	13	---	1,215,000
New	45	---	2,739,000	---		---
Supplemental	(8)	---	143,000	(4)	---	70,000
Subtotal	183	---	12,059,000	118	---	9,685,000
Special						
Environmental health sciences centers	7	---	5,270,000	7	---	5,644,000
Research career program	10	---	241,000	6	---	146,000
Scientific evaluation	---	---	32,000	---	---	37,000
Subtotal	17	---	5,543,000	13	---	5,827,000
Total Grants	200	---	17,602,000	131	---	15,512,000
Fellowships						
Non-competing	14	14	205,000	20	20	292,000
Competing	---	---	---	---	---	---
New	18	91	855,000	---	---	---
Supplemental	---	---	---	---	---	---
Subtotal	32	105	1,060,000	20	20	292,000
Training Grants						
Non-competing	17	211	2,215,000	10	122	1,453,000
Competing	---	---	---	---	---	---
New	---	---	---	---	---	---
Supplemental	---	---	---	---	---	---
Subtotal	17	211	2,215,000	10	122	1,453,000
Laboratory and clinical research			9,603,000			10,464,000
Research and development contracts			2,949,000			1,875,000
Research management and program services			1,508,000			1,517,000
Total			34,937,000			31,113,000

*Excludes 1973 appropriation restorations.

Justification

National Institute of Environmental Health Sciences

Authorizing Legislation: Public Health Service Act, Title III, Part A, Title IV, Part I

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	240	$5,160,000	238	$5,384,000	-2	+$224,000
Other expenses.....	---	29,777,000	---	25,729,000	---	-4,048,000
Total.....	240	34,937,000	238	31,113,000	-2	-3,824,000

General Statement

The National Institute of Environmental Health Sciences seeks to increase our understanding of the extent to which environmental agents can adversely affect man's health either immediately or over time. The results of the Institute's research are promptly made available to agencies having responsibility for environmental monitoring, standard setting, and control. The Institute seeks to determine the magnitude and significance of the hazard to man's health resulting from exposures to a wide range of concentrations of chemical, physical, and biological agents in the environment. Underlying mechanisms of adverse response are examined in order to determine the principles and generalizations which can provide the criteria needed to serve as a basis for the establishment of standards by those agencies charged with the regulatory responsibility in this area.

Among the beneficiaries of the basic knowledge developed by the Institute are those professionals concerned with the environmental components of human disease - e.g. - physicians treating poisonings by environmental chemicals, and medical teams concerned with the etiology of new diseases peculiar to certain locales or puzzled by drug interactions with environmental components. Our data are also useful to other programs dealing with environmental components of cancer, mutagenesis or heart and lung diseases (e.g. - National Cancer Institute, National Institute of Child Health and Human Development, National Heart and Lung Institute). Close liaison is maintained between the Institute and academic and medical communities as well. Liaison is also maintained between NIEHS and other Governmental agencies concerned with the environment -- Environmental Protection Agency, Food and Drug Administration, and National Institute of Occupational Safety and Health. Such contacts maintain awareness of programs, avoid unnecessary duplication of efforts, and foster supportive collaboration.

Extramural Research

Grant support of research in the environmental health sciences is an essential component of the national effort to identify, characterize, and ultimately deal with or regulate hazards in the environment. Fundamental data coming from research on environmental toxicants and their mechanisms of action suggest new solutions to the complex and growing problems of environmental contamination. As the information base expands and new techniques of measurement and analysis are developed, new approaches to realistic control methods or standards can be developed.

Intramural Research

The Institute's intramural program at NIEHS investigates the actions, interactions, and mechanisms of action of environmental components on biological systems including, where possible, the comparison of these effects with those in man. Such information is sought in order to provide a basis for the prevention, early diagnosis, and treatment of environmentally-related or affected diseases in man, and to establish the scientific basis for removal of agents from the environment.

The Institute's extramural and intramural programs are a blend of fundamental and applied research efforts applied to areas in which the state of knowledge justifies broad scale investigation. They, therefore, serve as a prime and unique focus for National and International efforts to deal with the effects of the environment on man's health.

The six research programs are: (1) Environmental Health Sciences Centers; (2) Environmental Mutagenesis and Reproductive Toxicology; (3) Etiology of Environmental Diseases and Disorders; (4) Environmental Pharmacology and Toxicology; (5) Environmental Pathogenesis; and (6) Intramural Laboratory and Clinical Research.

The narrative material which follows provides information about current and planned investigation, for support or conduct of research through grants, contracts, and in the Institute's own laboratories. The Institute's activities are discussed here in terms of programs. They are planned and operated as part of a total national program with each component complementary to the others, and all directed toward understanding of hazards to health resulting from man's interaction with his environment.

Environmental Health Sciences Centers

Authorizing Legislation: Public Health Service Act, Title III, Part A

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$5,270,000	---	$5,644,000	---	+$374,000
Total	---	5,270,000	---	5,644,000	---	+374,000

Introduction

The University-based Centers foster applications of expertise across disciplinary lines to environmental health problems. They are characteristically made up of groups of scientists who collaborate to develop fundamental and applied information about the causes and nature of environmental diseases in order to guide corrective and therapeutic programs. Because of the variety and complexity of environmental problems, several Centers with complementary spheres of interest are required to fulfill the national need. Accordingly, seven Centers, each with special expertise in one or more of the major categorical programs of the Institute, are supported. Collectively, they provide outstanding capabilities in traditional basic and applied disciplines vital to the Institute program including, among others, chemistry, cell biology, genetics, physiology, biostatistics, pharmacology, toxicology, pathology, epidemiology, behavioral sciences, nutritional science, occupational medicine, and chemical and environmental engineering.

Program Plans for 1975 and 1976

Each of the Centers, in accord with the specialties and research expertise of its staff, makes important contributions to the programs of the Institute. Their studies deal both with hazardous agents in the environment, which are the immediate focal points of public concern, and with specific diseases and disorders of environmental origin, which constitute the long-term basis for concern. Advances are being made in the identification and characterization of the sources, modes of entry, sites and basis of cell and tissue damage, and persistence of known and potential noxious agents. Important new data and insights are being developed regarding specific environmentally-related health problems, including chemical carcinogenesis; teratogenesis and other reproductive disorders; neural and behavioral anomalies; respiratory, circulatory, and kidney diseases; and fundamental aspects of toxicant metabolism and disruptive interactions at the molecular and cellular levels. Further advances are also being made in long-term population studies with emphasis on chemical epidemiology and on methodology for detecting early symptoms of fibrotic diseases of the lung, emphysema, and other disorders associated with exposure to environmental chemicals and dusts in the work or social environment.

The University-based Centers e national resources with concentrated expertise in areas of primary responsibility of the Institute. The new enter established in 1975 fills an important gap in diseases associated with mercury and other heavy metals in the environment. The ongoing Centers will continue their work in a wide range of environmental health problems.

Environmental Mutagenesis and Reproductive Toxicology

Authorizing Legislation: Public Health Service Act, Title III, Part A, Title IV, Part I

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$2,825,000	---	$1,770,000	---	-$1,055,000
Total	---	2,825,000	---	1,770,000	---	-1,055,000

Budget Mechanism:	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Regular	31	1,907,000	17	1,037,000	-14	-870,000
Special	1	25,000	0	0	-1	-25,000
Subtotal	32	1,932,000	17	1,037,000	-15	-895,000
Fellowships	5	113,000	2	25,000	-3	-88,000
Training grants	0	0	0	0	0	0
Research and development contracts	11	780,000	8	708,000	-3	-72,000
Total	48	2,825,000	27	1,770,000	-21	-1,055,000

Introduction

The mutagenesis and reproductive toxicology program deals with clarification of potential roles of chemical agents found in air, water, food and occupational situations, in changes in the genetic makeup of man, his reproductive capability, and in the development of the embryo or fetus. Induction of permanent changes in human genetic material is without question the most profound potential danger associated with environmental agents. In addition to anatomical defects generally ascribed to mutations, it is clear that subtle deficits in mental capacity and susceptibility to degenerative and infectious diseases also result from genetic aberrations. A major obstacle in assessing mutagenic potential of chemical agents has been the lack of rapid, inexpensive test systems with unequivocal quantitative relevance to man. This program is designed to fill this gap through development of sensitive test systems for detection and quantification of mutations.

Plans for 1975 and 1976

Advances are being made toward further understanding of the chemistry of molecular interactions between DNA and mutagenic agents such as azides, polychlorinated biphenyls (PCBs), nitroso compounds, vinyl chloride and other plastic intermediates.

The studies will provide an understanding of the molecular basis of changes in biochemistry and morphology and serve as a guide in devising test procedures to determine the frequency of mutations caused by different classes of mutagens. Efforts are being made to assess existing mutagenesis test procedures for relevance to man and toward development of new procedures. This is a high priority aspect of the program. The Institute recognizes serious deficiencies in available mutagenesis testing procedures, and in almost all cases the relevance of existing methodology to man at realistic mutagen levels is questionable. It recognizes also the necessity to establish valid tests as a basis for further and more rapid progress in this area. In line with this, new initiatives are being taken to interest the scientific community in applying the necessary effort and expertise for development of human mutagenicity test systems.

In reproductive toxicology the agents of primary concern are organophosphate and chlorinated hydrocarbon insecticides, PCBs, dioxins, mercurials, toxic fungal metabolites, vinyl chloride and other intermediates of important industrial processes. The studies range from efforts to establish causal relationships between toxicants and specific disorders to those designed to elucidate the molecular and cellular basis of hormonal changes and teratogenesis.

An important area of concern is the relationship between gestational periods and the nature and degree of damage induced in the fetus of experimental animals by certain pesticides and fungal toxins. These studies are designed to shed further light upon both the maximum risk time during gestation and the relationship between time of exposure and the nature of deformities in the offspring.

The importance of this program in maintaining the genetic fidelity of mankind and in assuring the conception and delivery of healthy babies now and in the future cannot be overemphasized. Thus, ongoing programs will be continued and efforts will be made during the coming year to bring the skills of geneticists and scientists in related fields in the university community to bear upon pressing problems in this area.

Etiology of Environmental Diseases and Disorders

Authorizing Legislation: Public Health Service Act, Title III, Part A, Title IV, Part I

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$6,030,000	---	$5,180,000	---	-$850,000
Total	---	6,030,000	---	5,180,000	---	-850,000

Budget Mechanism:	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Regular	60	4,386,000	34	4,012,000	-26	-374,000
Special	2	50,000	1	25,000	-1	-25,000
Subtotal	62	4,436,000	35	4,037,000	-27	-399,000
Fellowships	6	92,000	8	119,000	+2	+27,000
Training grants	6	598,000	2	162,000	-4	-436,000
Research and development contracts	6	904,000	6	862,000	0	-42,000
Total	80	6,030,000	51	5,180,000	-29	-850,000

Introduction

The central objective of the etiology program is to establish causal associations between human diseases and environmental chemicals and physical factors. It includes broad surveys to identify chemical agents now in use, or proposed for use, that have adverse effects upon biological systems. Concomitantly, it deals with description of specific malfunctions produced by these agents in body organs. This research provides a basis for clinical recognition of environmentally-related disorders in man, determination of their causes, and implementation of correct therapeutic and preventive measures. In a broader sense, it generates understanding of quantitative relationships between human diseases and noxious environmental agents. This will serve as a basis for management of current technology and future industrial development in such a way as to make them compatible with human health and well-being.

Program Plans for 1975 and 1976

Thousands of new chemicals are synthesized each year. Many of these are brought into large scale production alongside several hundred thousand already in use in industry, home and personal care products, pesticides, pharmaceuticals, fuel and food additives and a host of others. Despite increased efforts by manufacturers and government agencies to test new and existing compounds, the biological effects of many chemicals, physical factors, and combinations of these are unknown. Grantees are continuing to provide new insight into dose-disease relations for a broad range of agents.

By use of newly developed techniques and models, some pesticides have been found to disrupt nerve function and to influence behavioral and learning patterns. Though similar effects have not yet been demonstrated in man, the studies indicate the potential of these compounds to modify man's behavior. Further probing of the long-term effects of mercury and lead in the central nervous system has also revealed adverse effects on learning and behavior. The effects are seen in experimental animals which exhibit no visible lesions in the nervous system. Studies of this nature add a new dimension to problems of detection of cause-effect relations. They indicate the need to reassess our thinking in regard to meaningful dose-endpoint relations and in regard to appropriate environmental tolerance levels.

Research on the isolation and toxicity of natural and synthetic substances in food is being supported. Carcinogenic compounds and substances which cause blindness and kidney and lung damage were found in fungi that infest food grains. Aflatoxin, an extraordinarily potent carcinogenic by-product from certain fungi, was shown to cause cancer in fish through exposure of the eggs to the compound. Nitrites used as food preservatives were shown to react with sarcosine and other amines to form nitroso derivatives, a class of compounds known to be potent carcinogens and at least mild mutagens. This indicates the possibility of formation of carcinogens in the stomach by interaction of compounds in food and water.

The influence of heat, light, noise, microwaves, and laser radiation on human well-being is being investigated. Light was shown to enhance the acute toxicity of certain hepatotoxins such as aflatoxin, apparently through activation mechanisms in which riboflavin plays a role. Laser radiation was shown also to activate certain natural pigments. Activated forms of these pigments appear to be responsible for tissue lesions associated with laser radiation.

Work on air pollutants as etiological agents continues to produce new insight into diseases and disorders of the lungs and cardiovascular system. Ozone and nitrogen dioxide affect the lung lining through destruction of fatty substances. Sulfur dioxide from the air and sulfites used as food preservatives interact with some sulfur-containing compounds, forming thiosulfonates. These compounds circulate in the blood stream, slowly releasing sulfite throughout the body. Hydrazine, used in making a number of useful products, produces lesions characteristic of diabetes in experimental animals. Dichloroethylene, vinyl chloride and other compounds used in the plastics industry were found to be liver toxins and carcinogens which present considerable hazards to workers and perhaps others in the general population.

Further epidemiological studies on asbestosis revealed heretofore un-recognized dangers associated with asbestos inhalation. Cancer of the lungs and a rare cancer of the lung and abdominal linings, called mesothelioma, occur more frequently in insulation workers and others in building trades who are exposed to relatively small amounts of asbestos. Moreover, the probability of cancer may be increased up to 50-fold in these workers if they are also heavy smokers. These findings led to initiation of quantitative time-dose studies on the general population in urban areas, because residents of large cities are subjected to substantial levels of asbestos and other potentially carcinogenic air pollutants throughout their lives.

Further studies were carried out on the health effects of carbon monoxide. In addition to the limitations this gas imposes on the oxygen carrying capacity of the blood, high levels of carbon monoxide also alter blood flow to the abdominal region and may contribute to fatty accumulations in the blood and in arterial and heart muscles, thus aggravating preexisting cardiovascular disorders.

The importance of the agents and the scope of disorders indicated emphasize the necessity for continued effort to establish associations between these agents and disease and physiological stresses. Despite the difficulties of testing all environmental agents and combinations of agents, some new principles are beginning to emerge which permit cautious generalizations with respect to etiological relations of classes of compounds. This will materially reduce the burden of massive testing of individual compounds. Projects will be undertaken to further progress toward establishing such principles and generalizations. Work will also continue on the hazards of specific agents in carcinogenesis, teratogenesis, lung and cardiovascular diseases, neurotoxicity and other less debilitating but costly disorders and degenerative processes.

Environmental Pharmacology and Toxicology

Authorizing Legislation: Public Health Service Act, Title III, Part A, Title IV, Part I

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$7,965,000	---	$5,540,000	---	-$2,425,000
Total	---	7,965,000	---	5,540,000	---	-2,425,000

Budget Mechanism:	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Regular	71	4,575,000	59	4,083,000	-12	-492,000
Special	6	173,000	4	133,000	-2	-40,000
Subtotal	77	4,748,000	63	4,216,000	-14	-532,000
Fellowships	19	829,000	9	133,000	-10	-696,000
Training grants	9	1,263,000	7	1,034,000	-2	-229,000
Research and development contracts	5	1,125,000	3	157,000	-2	-968,000
Total	110	7,965,000	82	5,540,000	-28	-2,425,000

Introduction

The pharmacology-toxicology program is designed to develop understanding of the principles and mechanisms involved in toxicity of environmental agents. The research ranges from mechanistic studies of factors that alter the toxicity of chemical agents to studies on absorption, metabolism, and transport within the body. The nature and sites of defense systems and molecular targets associated with visible functional disorders are also being investigated. The goal is to provide a rational basis for maintaining, through environmental management, reasonable safety margins between environmental and body burdens of toxic agents in order to safeguard human health.

Program Plans for 1975 and 1976

Past work has shown that many organic compounds are susceptible to transformation by light, UV (ultraviolet) and other factors in the environment and by the action of various enzymes in the body. While nontoxic substances are generally formed, more toxic compounds are sometimes generated. Continuing studies show that aromatic petroleum products, common as air pollutants in urban areas, give rise to carcinogenic agents. Several pesticides, particularly aldrin and dieldrin, are converted to more toxic derivatives upon exposure to sunlight. These studies provide a clearer understanding of hazardous compounds in the environment and facilitate attempts to clarify toxicity mechanisms.

Further advances have been made toward understanding the clinical, pharmacological and biochemical aspects of lead and mercury intoxication. Lead impairs the operation of mixed function oxidases and, as a result, causes reduced metabolism of drugs and male hormones in lead-intoxicated children. In some cases, drug and hormone overload may present a health hazard.

New chelating agents effective in antagonizing the toxicity of methylmercury salts are being developed. Natural defense systems against heavy metals have also been demonstrated. At least four proteins have been identified which form strong complexes with cadmium, lead and mercury. These appear to play a part in combating heavy metal toxicity and may provide a useful means of protection against the hazards of heavy metal exposure.

Studies are continuing on the nature of drug metabolizing enzymes. These enzymes generally detoxify foreign agents and make them more readily excreted through the kidneys. However, in some cases, the same enzymes activate carcinogenic agents, such as benzpyrene and aflatoxin, and increase the likelihood of cancer. Attempts are being made to gain further insight into the mechanisms that regulate these activities.

Understanding of the movement and sites of action of toxic agents is vital in establishing the risk-benefit equation in modern technology. New projects will continue to focus on transformations of compounds in order to understand the nature of proximal toxicants and their subsequent effects on cellular and tissue targets. In many cases, interactions between combinations of compounds result in dangerous enhancement of toxicity even at levels at which the individual agents are normally considered to present no risk to man. Such interactions must be identified and assessed for their consequences in relation to long-term health problems and the risk of birth defects and genetic change in future generations.

Concern exists as to what health effects, if any, are associated with continued oral exposure to various asbestiform types. In response to this concern, the Congress added $1,000,000 to the budget request for 1975 and directed that the Institute initiate a long-term study on the effects of ingested asbestos. Two contracts are planned for 1975 to study these health effects -- one is a lifetime ingestion study in rats, utilizing 4 specific asbestiform types, and the other is a lifetime ingestion study in hamsters, utilizing 2 or 3 specific asbestiform types.

Environmental Pathogenesis

Authorizing Legislation: Public Health Service Act, Title III, Part A, Title IV, Part I

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$1,736,000	---	$998,000	---	-$738,000
Total	---	1,736,000	---	998,000	---	-738,000

Budget Mechanism:	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Regular	21	1,191,000	8	553,000	-13	-638,000
Special	1	25,000	1	25,000	0	0
Subtotal	22	1,216,000	9	578,000	-13	-638,000
Fellowships	2	26,000	1	15,000	-1	-11,000
Training grants	2	354,000	1	257,000	-1	-97,000
Research and development contracts	3	140,000	3	148,000	0	+8,000
Total	29	1,736,000	14	998,000	-15	-738,000

Introduction

The pathogenesis program focuses upon the details and time sequence of molecular and cellular events that culminate in recognizable diseases and end-points upon exposure to toxic agents. Because of the wide range of chemical agents and physical factors present, no organ or body function can be considered invulnerable. Diseases of the pulmonary and cardiovascular systems, the liver, kidneys, reproductive system, digestive tract, the central and peripheral nervous systems, and degenerative disorders of complex and long-term etiology have been documented and related to one or more environmental agents. Additionally, the program is intended to clarify the interactions through which environmental agents play a secondary or ancillary role in the progress of degenerative disorders. Knowledge of initial or very early molecular and cellular lesions and understanding of their role in pathological endpoints offers the best hope, apart from prevention of toxic exposures, for detecting and countering the development of diseases before damage in target organs becomes irreversible.

Plans for 1975 and 1976

Studies on the biologic effects of radiation have led to development of lighting systems that closely simulate natural noon sunlight. This has permitted critical experiments in phototoxicity and light-induced cancer. As a result, new insights into the induction and potentiation of such cancer by chemical agents are being developed. Similar studies are underway to assess the role of light intensity and quality in photosensitization phenomena in skin diseases and allergies.

Studies are underway currently to assess the long-term effects and mechanisms of heat stress, dehydration, microwaves and other physical factors in aging and degenerative diseases associated with aging.

Studies were carried out on the process of transition from normal to cancerous cells and the possible role of various environmental factors in the transition. The findings indicate that cancer formation may involve several rather distinct steps: the first step is called initiation, which may result from a somatic mutation; the second is a promotion phase, in which normal suppression of cell division no longer prevails; and the third is a phase of rapid cell growth. The promotion stage can be inhibited by proteases, which suggests that a protein is involved in tumorigenesis and that ways might be found to block cancer formation at this stage.

Studies have been conducted on pathogenesis induced by heavy metals. They show that lead accumulates at the endplate region of the juncture between nerve and muscle fibers, blocking electrical impulses and preventing transmission of messages from the brain to the muscle. Both lead and mercury damage the sheath in nerve fibers and destroy the selectivity in passage of substances from the blood into the brain, thereby disrupting the chemical balance in the central nervous system. These studies help to clarify the basis of the behavioral and learning aberrations characteristic of lead and mercury poisoning of long duration.

Similar studies on renal disorders induced by these metals and their compounds show disruption of selective resorption processes and interference in energy metabolism and protein synthesis. This may account for malfunction in the resorptive mechanism.

Important contributions are being made toward understanding fibrotic diseases of the lungs, including asbestosis and berylliosis. Triggering of connective tissue biosynthesis appears to be the first step in these diseases. It was shown that beryllium forms an antigenic complex with normal lung protein, which gives rise to fibrotic lesions. Other basic studies reveal that certain dusts and chemicals of environmental origin destroy the normal antiproteinase factors in the lungs, permitting over-activity of protein digesting enzymes. This presumably leads eventually to digestion of vital lung tissues and results in emphysema.

Many other fundamental studies are currently underway to determine effects of environmental chemicals and dusts on cilia and lung macrophages in the respiratory tract and the consequences of inactivation of these cells in terms of development of chronic bronchitis, emphysema, fibrosis and other lung disorders.

Although considerable progress has been made, much remains to be done to develop a clear understanding of all ramifications of environmental agents in acute and chronic disease development. New and ongoing projects will continue to focus on these problems.

Intramural Laboratory and Clinical Research

Authorizing Legislation: Public Health Service Act, Title III, Part A,

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	202	$4,363,000	200	$4,573,000	-2	+$210,000
Other expenses.....	---	5,240,000	---	5,891,000	---	+651,000
Total.....	202	9,603,000	200	10,464,000	-2	+861,000

Introduction

The intramural research program is directed toward development of a reliable data base for use in establishing standards and devising remedial methods in a variety of populations at risk from exposure to environmental and occupational chemicals and physical factors. The Institute is fostering research at the fundamental level on a wide range of environmental agents and on the mechanisms of acute and long-term effects of these agents on man. The program is focused on several environmental problems which, on the whole, present the greatest potential hazard to the present population and future generations. These include airborne toxicants, metal toxicants, pesticides, mutagenic compounds, physical factors, and non-categorical hazardous compounds.

Plans for 1975 and 1976

The studies on airborne toxicants focus on compounds which generally gain entry into the body through the lungs, although entry through the skin and gastrointestinal tract may also occur as a result of settling on the skin and into food and water supplies. Numerous human diseases and disorders from exposure to such agents are now well established. These include berylliosis, asbestosis, emphysema, chronic bronchitis, lung cancer, cardiovascular diseases, and reproductive disorders and fetal anomalies. A portion of intramural facilities are devoted to special monitoring and metering devices for conducting long-term studies on the interrelationships between airborne agents and lung disorders in experimental mammalian models.

Several scientists are developing basic information about the sites and mode of action of heavy metals. Special attention has been given to mercury and lead and their compounds, and the neurological and teratogenic effects of these substances.

Intensive efforts have been made to clarify the many aspects of pesticide interactions in mammalian systems. Pesticides are an extremely diverse group of compounds with widely differing chemical structures and properties. Not surprisingly, therefore, they exhibit a broad spectrum of biological activities ranging from general toxicity to specific targeted action on nerve tissues and often on specific enzymes and processes. Institute scientists have concerned

themselves with all aspects of pesticide toxicology, including structure-activity relationships, metabolism, pharmacodynamics, mechanisms of action, and mechanisms of toxication and detoxication. Considerable effort has been devoted also to clarification of joint action of the various compounds on concomitant multiple exposure in disorders such as birth defects, carcinogenesis, mutagenesis, and general toxicity.

As part of the Institute's overall efforts in the area of mutagenesis, the intramural efforts have been greatly intensified. Work is continuing at an accelerated pace on the nature of mutagens and their interactions with DNA. Special emphasis is placed upon development of *in vivo* test procedures which will detect point mutations and can be used to bridge the gap between test models and mutation frequency and susceptibility in man. This is a high priority goal of the Institute and maximum effort will continue in this work.

Progress has been made toward establishing quantitative relationships between biological effects of physical factors in the field of noise, microwaves, and radiation. Because of the paucity of research in these areas and the importance of these factors in human well-being, work in the intramural program is being expanded.

The intramural program provides the vehicle for direct research to deal with problem areas and specific problems vital to the national interests and to the fulfillment of Institute responsibilities where sufficient effort and interest is not available elsewhere in the scientific community. In many instances, projects and research developments within the intramural program serve as a catalyst to the scientific community at large. Work will continue in the areas indicated and new projects, especially in mutagenesis and in physical factors, will be added as funds and additional manpower become available.

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Research Management and Program Services

Authorizing Legislation: Public Health Service Act, Title III, Part A,

	1975 Base		1976		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	38	$797,000	38	$811,000	0	+$14,000
Other expenses	---	711,000	---	706,000	---	-5,000
Total	38	1,508,000	38	1,517,000	0	+9,000

Introduction

This activity supports the Office of the Director and the Office of the Associate Director for Extramural Programs and provides for the overall administration, coordination, and direction of the varied programs and activities of the Institute. The Office of the Director provides for the planning, direction, management, and coordination of all Institute activities; the review of current and proposed programs; the introduction of new knowledge into currently operating programs; and the provision and supervision of centralized administrative services. The Office of the Associate Director for Extramural Programs is responsible for the scientific and administrative management of the Institute's grants program. This includes the review and evaluation of research, fellowship and training grant applications for presentation to the Institute's Advisory Committees, and liaison with applicants, grantees, advisory bodies, other components of the National Institutes of Health and the Department of Health, Education, and Welfare, and other interested organizations.

Program Plans for 1975 and 1976

The Office of the Director will continue to devote most of its resources to the selection of the research questions which most need investigation and to the planning and direction of the total programs of the Institute. In addition, the Director serves as the American Coordinator of the Environmental Health Sciences portion of the US-USSR Health Agreement. Exchanges of scientists under this agreement have begun and will continue in 1976. The Director also serves as Project Chairman of the US-USSR Working Group on the Biological and Genetic Effects of Pollutants. In addition, the Director serves as Chairman of the DHEW Committee to Coordinate Toxicology and Related Programs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Environmental Health Sciences Centers
(Public Health Service Act, Title III, Part A)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$5,270,000	Indefinite	---	$5,644,000

Purpose: The University-based Centers were created to integrate the efforts of scientists in several traditional disciplines and foster application of expertise across disciplinary lines to environmental health problems.

Explanation: Because of the variety and complexity of environmental problems, several Centers with complementary spheres of interest are required to fulfill the national need. Accordingly, seven Centers, each with special expertise in one or more of the major categorical programs of the Institute, were supported in FY 1975. Collectively, they provide outstanding capabilities in traditional basic and applied disciplines vital to the Institute program. The Centers are characteristically made up of groups of scientists who collaborate to develop fundamental and practical information about the causes and nature of environmental diseases in order to guide corrective and therapeutic programs. Their areas of expertise include, among others, chemistry, cell biology, genetics, physiology, biostatistics, pharmacology, toxicology, pathology, epidemiology, behavioral sciences, nutritional science, occupational medicine, and chemical and environmental engineering.

Accomplishments in 1975: Each of the Centers has made important contributions to the objectives of the Institute. Their studies deal with a wide variety of hazardous agents in the environment which are the immediate focal points of public concern and with specific diseases and disorders of environmental origin. Advances have been made in the identification and characterization of the sources, modes of entry, sites and basis of cell and tissue damage, and persistence of known and potential noxious agents. These include vinyl chloride, bis(chloromethyl)ether, and asbestos. Important new data and insights have been developed regarding specific environmentally-related health problems, including chemical carcinogenesis; teratogenesis, and other reproductive disorders; neural and behavioral anomalies; respiratory, circulatory, and kidney diseases; and fundamental aspects of toxicant metabolism and disruptive interactions at the molecular and cellular levels. Further advances are being made in long-term population studies with emphasis on chemical epidemiology and on methodology for detecting early symptoms of fibrotic diseases of the lung, emphysema, and other disorders associated with occupational or accidental exposure to environmental chemicals and dusts. Particular emphasis is being directed in some Centers toward potential health problems that may arise from new and intensified activities in technologies related to energy production and conservation. One new Center with outstanding expertise and research capabilities in chemistry and hazards of mercurials and other heavy metals was added in 1975.

Objectives for 1976: The budget request provides for funds to continue support of the 7 Centers funded in 1975.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Environmental Mutagenesis and Reproductive Toxicology
(Public Health Service Act, Title III, Part A, Title IV, Part I)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$2,825,000	Indefinite	---	$1,770,000

Purpose: This program aims at clarification of the nature and structure-activity relations of chemical agents capable of altering the genetic makeup of man, his reproductive capability, and development of the embryo or fetus. A further aim is to develop mutagenicity test systems with unequivocal quantitative relevance to man.

Explanation: A major effort in this program is being made in the Institute's laboratories. However, this is supplemented to a considerable degree through individual, program and center grants. The studies will provide an understanding of the molecular basis for visible changes in biochemistry and morphology due to mutagenic and teratogenic agents. Efforts are being made also to assess existing mutagenesis test procedures for relevance to man and toward development of new procedures. This is a high priority aspect of the program. Serious deficiences in present test systems must be bridged to facilitate progress toward assessment of environmental agents, food additives and natural products for mutagenic potential in man.

Accomplishments in 1975: Progress is being made toward further understanding of the chemistry of molecular interactions between DNA and mutagenic agents such as cyclamates, saccharin, azides, nitroso compounds, nitrites and PCBs. Studies in reproductive toxicology range from efforts to establish etiological relationships between toxicants and specific disorders to those designed to elucidate the molecular and cellular basis of teratogenesis and hormone changes. The agents of primary concern are widespread compounds such as chlorinated hydrocarbon and organophosphate insecticides, fungal metabolites, dioxins, mercurials, lead, cadmium and other heavy metals, and a number of pharmaceuticals and industrial intermediates, including vinyl chloride.

Further light has been shed on the gestational period during which the fetus is at maximum risk upon exposure of the mother to toxicants such as heavy metals, parathion, and certain mycotoxins. Progress has been made in the development of better teratology and fetal test systems in experimental animals. These methods include techniques for culture of fertilized eggs and fetuses from several species. The embryo or portions of it can be exposed to precise amounts of test compounds for exact periods of time at any desired stage of development. This and similar techniques will be extremely valuable in future efforts to identify critical cells in specific types of birth defects and in predicting the action of new and existing compounds with liabilities as teratogens. Such capability should notably enhance the effectiveness of preventive medicine in this area.

Objectives for 1976: The budget request provides for continued research on environmental compounds as they influence man's genetic makeup, his reproductive capability, and the healthy development of future generations.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Etiology of Environmental Diseases and Disorders
(Public Health Service Act, Title III, Part A, Title IV, Part I)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$6,030,000	Indefinite	---	$5,180,000

Purpose: The central objective of the etiology program is to establish causal associations between human diseases and noxious chemical and physical factors in the environment. This involves description and characterization of pathological lesions and endpoints in specific target organs and inter-dependent physiological systems.

Explanation: This program is carried out both by the intramural staff and through grants and contracts. Thousands of new chemicals are synthesized each year. Many of these are brought into production, adding to the thousands already in use in industry, to make home and personal care products, food and fuel additives, pesticide and pharmaceutical preparations, and a host of others. Despite increased efforts by manufacturers and government agencies to test new and existing compounds, the biological effects of many of these substances alone and in combinations are still unknown. The research is designed to provide a sound basis for clinical recognition of environmentally-related disorders of man and their causes and for implementation of correct therapeutic and preventive measures. In a broader sense, its aim is to provide a foundation for wise management of current technology and future industrial development in order to make them compatible with human health and well-being.

Accomplishments in 1975: Evidence has been obtained that several widely used pesticides disrupt nerve function and may influence behavioral and learning patterns, induce cancer and interfere in reproduction. Further probing of the long-term effects of lead and mercury on the central and peripheral nervous systems reveals adverse effects on learning and behavior even before visible damage to the nervous system is evident. The carcinogenic activities of industrial dust such as asbestos, have been investigated further and new evidence of synergism between particulates and cigarette smoking has been obtained. An important new class of carcinogens, alkane and alkene chlorides, have been uncovered and work is now in progress on their mechanisms of action. New toxins have been detected in fungi often associated with grains and other food staples. The different toxins cause a variety of syndromes ranging from carcinoma and edema of the lungs to photosensitization and neurological and kidney damage. Advances are being made in understanding the influence of heat stress, light, noise, microwaves and laser radiation on physiological systems. New insights are being developed into disorders of the lungs and cardiovascular systems induced by ozone, oxides or nitrogen and sulfur, and by industrial dusts from coal, plastics, asbestos, textiles and others. Epidemiological studies provide evidence that cancer, fibrotic diseases, emphysema and bronchitis are often greatly enhanced by cigarette smoking and inhalation of lung irritants characteristic of urban atmospheres.

Objectives for 1976: The budget request provides for continued research on chemical, physical and biological agents in the environment that may act, singly or in combination, as progenitors of human disease.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Environmental Pharmacology and Toxicology
(Public Health Service Act, Title III, Part A, Title IV, Part I)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$7,965,000	Indefinite	---	$5,540,000

Purpose: The pharmacology-toxicology program is designed to develop understanding of the principles and mechanisms involved in the toxicity of environmental agents. Its further aim is to characterize the nature and sites of molecular, cellular and tissue interactions with toxicants and to relate these to functional disorders.

Explanation: These studies are carried out both within the Institute's laboratories and through individual grants and contracts and program and center grants. Work in several laboratories focuses on the nature and basic mechanisms of chemical transformations of environmental agents in the environment and in the body. A major segment of the program deals with inherent defense systems such as binding, exclusion, storage, metabolic and clearance systems. Substantial effort is devoted also to clarification of interactions between specific enzymes and metabolic targets responsible for gross manifestations of toxicity. The goal is to provide a rational basis for maintaining, through environmental management, reasonable safety margins between environmental and body burdens of toxic agents in order to safeguard human health now and in future generations.

Accomplishments in 1975: The nature of drug metabolizing enzymes and their roles in transformation of toxic chemicals, in body clearance, and in activation of carcinogenic agents have been clarified in large part, and the groundwork has been laid for more rapid progress in understanding pathogenesis mechanisms. The processes of deposition, absorption and transfer of a number of hazardous agents have been elucidated. These processes determine the load of foreign substances with which the body must cope. Storage, toxication-detoxication and excretion, which are gross indicators of how the body copes with foreign agents, have been clarified in many cases. Studies on the processes of enzyme induction, repression, and qualitative and quantitative aspects of metabolism have contributed substantially to understanding of toxicity endpoints and differences in responses to specific agents due to age, sex, species, nutrition, current and antecedent diseases, and enzymatic, immunologic and genetic factors. In response to Congress' directive that the Institute initiate a long-term study on the effects of ingested asbestos, two research contracts are being awarded in 1975 to study these effects. One contract is a lifetime ingestion study in rats, utilizing 4 specific asbestiform types, and the other contract is a lifetime ingestion study in hamsters, utilizing 2 or 3 specific asbestiform types.

Objectives for 1976: The budget request provides for continued pharmacological and toxicological studies of environmental agents as they enter the body, are distributed, and as they disrupt the normal functions and structures of the body.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Environmental Pathogenesis
(Public Health Service Act, Title III, Part A, Title IV, Part I)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,736,000	Indefinite	---	$998,000

Purpose: The pathogenesis program deals with the details and time sequence of molecular and cellular events that culminate in recognizable diseases and other endpoints upon exposure of individuals to toxic agents.

Explanation: This work is carried out both in intramural laboratories and through grants and contracts. Diseases of the pulmonary and cardiovascular systems, the liver, kidneys, reproductive system, and degenerative disorders of long-term and complex etiology have been well documented and related to environmental factors. The program is designed to develop knowledge of initial or very early molecular and cellular lesions that will facilitate implementation and improve the effectiveness of prophylactic or therapeutic measures.

Accomplishments in 1975: Further insight has been provided into the lesions caused by lead and mercury in the peripheral and central nervous systems. Damage to the sheath in nerve fibers and damage to structures constituting the blood-brain barrier provide understanding of lead brain damage which is common in lead-poisoned children, and of persistent changes in learning and behavioral patterns of such children. The basis of lung fibrosis from exposure to agents such as coal dust and asbestos has been clarified in large part through studies of immunology. The relationship between cancer and other diseases of the lung and industrial dusts and irritant gases have been considerably illuminated through basic studies of inhibition of lung defense mechanisms.

Recent pharmacological studies on carcinogens have led to better correlations between structures of numerous compounds and carcinogenesis. It is now apparent that environmental agents such as benzpyrene and chlorinated hydrocarbon pesticides are activated through metabolism. Studies of structure-activity relations of the metabolites show good correlation with cancer induction whereas little correlation could be established with the parent compounds. This now simplifies the study of carcinogenesis because the molecular interactions of the primary carcinogen can be followed. Analogous studies on metabolites of other compounds that produce other types of pathological lesions have also been enhanced by understanding of the primary toxicant. Examples include carcinogenesis by nitroso compounds derived in the stomach from nitrites and hepatotoxicity resulting from the action of oxygenated derivates of chlorinated alkanes and alkenes such as vinyl chloride, ethylene dichloride and carbon tetrachloride.

Objectives for 1976: The budget request provides for continued research on the initial or very early molecular and cellular lesions that lead to human environmental diseases or the complication of pre-existing health problems.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Intramural Laboratory and Clinical Research
(Public Health Service Act, Title III, Part A)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
202	$9,603,000	Indefinite	200	$10,464,000

Purpose: The intramural research program was created for the purpose of investigating at the fundamental level the long term overt and subtle effects of chemical and physical environmental factors potentially hazardous to man, without limitations regarding the origin or sources of such factors.

Explanation: The laboratory and clinical research program consists of six branches concerned with directed fundamental research. Three of these have additional responsibilities for research support. The overall goal is to develop a reliable data base for use in establishing standards and devising remedial measures in a variety of populations at risk from exposure to environmental and occupational chemicals and physical factors. The programs focus especially on toxicology and pharmacology, reproductive biology, mutagenesis and pathology. Support in synthetic and analytical chemistry, in biomedical instrumentation design and development, in computer technology, and administrative and clerical services are provided.

Accomplishments in 1975: Considerable effort has been devoted to development of basic information regarding the sites and mode of action of heavy metals. Notable advancements are being made in understanding of the biochemical and structural basis of neurological and teratogenic effects of lead and mercury. Progress is being made toward elucidation of structure-activity relations, metabolism, pharmacodynamics, mechanisms of action and mechanisms of detoxication and toxicity enhancement of pesticides. New light has been shed on the role of individual compounds and combinations of factors in birth defects, reproductive disorders and carcinogenesis. Efforts in mutagenesis research are being intensified, with development of new insight into the nature of mutagens, their sites and modes of interaction with DNA, and their effects on DNA repair systems. Refinements are being made in the host mediated assay and other test systems for mutagenicity. Work has been expanded and progress is being made toward establishing quantitative relationships between biological effects and physical factors such as noise, microwaves and radiation. In addition to the indicated research activities, the administration and staff organize and sponsor workshops and conferences for gathering information on specific subjects and assessing the state of the art in several areas of vital concern to the Institute.

Objectives for 1976: The total increase of $855,000 contains $151,000 for built-in requirements and $704,000 for a program increase. This increase would permit the expansion of our intramural research program, particularly in the area of environmental mutagenesis and reproductive toxicology.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Research Management and Program Services
(Public Health Service Act, Title III, Part A)

1975			1976	
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
38	$1,508,000	Indefinite	38	$1,517,000

Purpose: This activity supports the Office of the Director and the Office of the Associate Director for Extramural Programs and provides for the overall administration, coordination, and direction of the varied programs and activities of the Institute.

Explanation: The Office of the Director provides for the planning, direction, management, and coordination of all Institute activities; the review of current and proposed programs; the introduction of new knowledge into currently operating programs; and the provision and supervision of centralized administrative services. The Office of the Associate Director for Extramural Programs is responsible for the scientific and administrative management of the Institute's grants program. This includes the review and evaluation of research, fellowships and training grant applications for presentation to the Institute's Advisory Committees, and liaison with applicants, grantees, advisory bodies, other components of the National Institutes of Health and the Department of Health, Education, and Welfare, and other interested organizations.

Accomplishments in 1975: During 1975, the Office of the Director devoted a significant portion of its resources to the selection of the research questions which most need investigation and to the planning and direction of the total programs of the Institute. In addition, the Director serves as the American Coordinator of the Environmental Health Sciences portion of the US-USSR Health Agreement. Exchange of scientists under this agreement have begun and will continue in 1976. The Director also serves as Project Chairman of the US-USSR Working Group on the Biological and Genetic Effects of Pollutants. In addition, the Director serves as Chairman of the DHEW Committee to Coordinate Toxicology and Related Programs. The Extramural program staff advanced its effort to strengthen its liaison and management activities in order to obtain maximum benefits from the available grant funds.

Objectives for 1976: The Office of the Director will continue to devote most of its resources to the selection and assignment of priorities to research questions and to the planning and direction of the Institute's programs. The Extramural program staff will maintain surveillance over approximately 200 grants during this year.

DEPARTMENT OF HEALTH EDUCATION AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$31,113,000	$7,760,000
Total obligation	31,113,000	7,760,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Environmental health sciences centers	---	$5,644,000	---	$2,022,000
Environmental mutagenesis and reproductive toxicology	---	1,770,000	---	654,000
Etiology of environmental diseases and disorders	---	5,180,000	---	767,000
Environmental pharmacology and toxicology	---	5,540,000	---	628,000
Environmental pathogenesis	---	998,000	---	424,000
Intramural laboratory and clinical research	200	10,464,000	200	2,875,000
Research management and program services	38	1,517,000	38	390,000
Total obligations	238	31,113,000	238	7,760,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	238	238
Full-time equivalent of all other positions	107	107
Average number of all employees	341	341
Personnel compensation:		
Permanent positions	$3,898,000	$985,000
Positions other than permanent	855,000	215,000
Other personnel compensation	115,000	30,000
Subtotal, personnel compensation	4,868,000	1,230,000
Personnel benefits	516,000	130,000
Travel and transportation of persons	350,000	115,000
Transportation of things	32,000	9,000
Rent, communications and utilities	1,085,000	310,000
Printing and reproduction	65,000	18,000
Other services	1,991,000	570,000
Project contracts	1,875,000	575,000
Payment to NIH Management Fund	834,000	208,000
Supplies and materials	1,540,000	485,000
Equipment	700,000	190,000
Grants, subsides and contributions	17,257,000	3,920,000
Total obligations by object	31,113,000	7,760,000

Justification

The estimate for the three-month interim period reflects a continuation of the program of the National Institute of Environmental Health Sciences consistent with the 1976 Estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 Estimate.

RESEARCH RESOURCES

WITNESSES

DR. THOMAS G. BOWERY, DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DR. JAMES F. O'DONNELL, ASSISTANT DIRECTOR, DIVISION OF RESEARCH RESOURCES
DAVID L. CHICCHIRICHI, EXECUTIVE OFFICER, DIVISION OF RESEARCH RESOURCES
BERTIL G. BERGQUIST, BUDGET OFFICER, DIVISION OF RESEARCH RESOURCES
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD J. FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We will continue with the National Institutes of Health. We now have the Division of Research Resources.

The presentation will be made by Dr. Thomas G. Bowery, the Director, and we will insert in the record your biographical sketch, Dr. Bowery.

[The biographical sketch follows:]

BIOGRAPHICAL SKETCH

Name: Thomas G. Bowery.

Position: Director, Division of Research Resources.

Birthplace and date: Bellevue, Pa., December 17, 1921.

Education: B.S., Michigan State University, 1943; M.S., Rutgers University, 1948; Ph. D., Rutgers University, 1951.

Experience: Director, Division of Research Resources, 1969–present.

Acting Director, Division of Research Resources, 1968–69.

Associate Director for Operations, Division of Research Facilities and Resources, National Institutes of Health, 1967–68.

Assistant Chief for Operations, Division of Research Facilities and Resources, NIH, 1965–67.

Extramural Operations and Procedures Office, Office of the Director, NIH, 1964–65.

Special Assistant to the Associate Director for Research Grants, Office of the Director, NIH, 1963–64.

Grants Associate, Division of Research Grants, NIH, 1962–63.

Research professor, department of entomology, North Carolina State College, Raleigh, N. C., 1959–62.

Research associate professor, department of chemistry, North Carolina State College, Raleigh, N. C., 1953–59.

Research assistant professor, pesticide residue laboratory, Everglades Experiment Station, University of Florida, Belle Glade, Fla., 1951–52.

Research associate in chemistry, office of the State chemist, New Jersey Agricultural Experiment Station, New Brunswick, N. J., 1948–51.

Research Fellow, entomology department, Rutgers University, New Brunswick, N. J., 1946–48.

Association memberships: American Association for the Advancement of Science; American Chemical Society; Sigma Xi.

Publications: Author of some 23 publications in seven journals.

Mr. FLOOD. Do you have some people with you you want us to know?

Dr. BOWERY. Yes; Mr. Chairman.

To my immediate left is Mr. David Chicchirichi, our executive officer. To his left is Mr. Bergquist, our budget officer, and to his left is Dr. James O'Donnell, our assistant director.

Mr. FLOOD. All right.

You have a prepared statement. How are you going to handle this, Doctor?

Dr. BOWERY. I would like to read it into the record, sir, and then answer any questions you may have.

Mr. FLOOD. All right, suppose you do.

GENERAL STATEMENT

Dr. BOWERY. Mr. Chairman and members of the committee, it is a pleasure to speak to you again about the programs of the Division of Research Resources. I would like to cover several points related to changes that are taking place within the Division and explain to you in some detail the objectives of the Division.

During the past year, the Division has been working on improving the effectiveness and impact of the Division's programs on those activities being supported by the individual categorical Institutes of the NIH. During 1975, and this will continue into 1976, we initiated a series of interfacing sessions with the Director and key staff members of each of the individual Institutes. The purpose of these sessions is two-fold—to provide an opportunity for more complete exposure of ongoing and planned activities of the Division's resource programs and to acquire additional knowledge regarding the scientific research activities of each of the Institutes. These sessions have already identified areas where the Division and the Institutes can work more closely together to make the programs of each more effective and efficient.

Another activity which parallels the interfacing process has been the review and updating of the basic objective of the Division. In 1961, the Division was established with the objective to support general purpose facilities and resources and strengthen the general health research capabilities of institutions. In 1974, after a number of months of intensive self-study, the DRR established as its contemporary objective to identify and meet the research resource needs and opportunities of the NIH by conceiving, creating, developing, and assuring the availability of those resources that are essential for the effective conduct of biomedical research. An important point is that the Division's role in biomedical research is directed toward participation in the acquisition of new scientific knowledge by providing those physical and human resources needed on a multicategorical basis which are necessary for the conduct of biomedical research supported by the categorical Institutes and other funding agencies. In other words, the Division's role is a critical supportive one. We feel that much of the research which is being conducted in the country today either could not be done at all or would be done less effectively and efficiently without the resources which have been conceived, created, developed, and made available by the Division of Research Resources.

I would now like to briefly discuss each of the six programs which are administered by the Division. I will not go into great detail since they are described within the justifications before you.

CLINICAL RESEARCH

The clinical research program, which has been in operation for a decade and a half, currently provides approximately 80 percent of the research patient beds supported extramurally by the National Institutes of Health. Much of the important clinical research in the areas of transplantation, diabetes, kidney disease, digestive diseases, cancer therapy, and others conducted in the country during the past 15 years, has been performed within these general clinical research centers. Approximately half of the existing 84 centers have established outpatient departments. The impact of this is the ability to conduct a great deal of clinical research not requiring the hospitalization of the subject and at much less cost. In 1975 it is estimated that approximately 215,000 patient days will be supported by the program, together with about 42,000 outpatient visits. Approximately 12,000 individuals will use these centers during 1975. Included in this group are physicians, nurses, laboratory personnel, recreational and occupational therapists, clinical investigators, resident physicians, dietetic interns, as well as medical students, interns, and student nurses who are receiving "real life" training within the centers.

BIOTECHNOLOGY RESEARCH

The biotechnology research program provides biomedical investigators access to highly sophisticated and often expensive instruments and methodologies, and staff who are expert in their use. It also permits the exploitation of new and advanced technologies which are evolving at an extremely fast rate. Because of the complexity and high cost of these types of resources, we have begun a concerted effort to make these resources shareable among and between institutions heavily engaged in biomedical research.

For example, in 1973 the Division supported the establishment of two 1 million volt electron microscope facilities which are entirely dedicated to biomedical research. In establishing these centers we worked with the institutions involved, the University of Wisconsin and the University of Colorado, to insure that investigators from elsewhere throughout the country had access to as much as 50 percent of the beam time available on these expensive resources. The impact of such an arrangement is to diffuse the capabilities of this advanced technology into institutions which have a need for such capabilities but lack the necessary scientific base and the required staffing and space resources to justify the resources on their own.

As we emphasize and develop resource sharing arrangements in other biotechnology resources these facilities will become more readily available to a broader range of investigators at lesser cost.

CHEMICAL/BIOLOGICAL INFORMATION HANDLING

The chemical/biological information handling program, utilizing a DRR developed computer system called PROPHET, was initiated approximately 5 years ago for the purpose of developing computer tools for research uses such as predicting the actions of drugs on the central nervous system through analyses of their molecular shapes and

electronic properties. The system became operational in October of 1973 and is being used in a number of areas of investigation related to drug research. Examples of where this system is being used include analyzing the structure of antibodies in order to understand the chemical and genetic mechanisms underlying immunity; studying the three dimensional shapes of cancer-relevant steroids and relating these structural features to the observed biological activity of these drugs; studying how the body handles alcohol and other drugs of abuse; and exploring the uses of computer methods in managing research records of human patients in the clinical pharmacology area.

The PROPHET system is currently being utilized by nine user groups in Massachusetts, Pennsylvania, Illinois, the State of Washington, Connecticut, Maryland, and several locations in New York. It is anticipated that the number of user groups will increase by about four each year over the next several years.

LABORATORY ANIMAL SCIENCES AND PRIMATE RESEARCH

One of the major problems that we have encountered within the laboratory animal sciences and primate research program is the decrease in the number of primates available for biomedical research within the United States. Several steps have been taken to alleviate this problem. The National Institutes of Health has established a primate steering committee. I am a member of that committee. This group is closely monitoring the primate supply problem and is developing plans to lessen its impact on the programs of the NIH and other health agencies. In addition, the Division has awarded several contracts to commercial firms to study the feasibility of domestically breeding primate species needed for research purposes, and we are encouraging each of the seven national primate centers to initiate or expand their breeding operations so that they, hopefully, can produce 100 percent of the primates required for the conduct of their own research.

The laboratory animal sciences program has also been deeply involved for the last several years in the funding of institutional improvement activities which are necessary for compliance with the Animal Welfare Act of 1970. Since fiscal year 1972 when Congress specifically appropriated funds for this activity, $9.6 million has been awarded to approximately 85 institutions which have used these funds to upgrade their animal facilities.

MINORITY BIOMEDICAL SUPPORT

The minority biomedical support program, which was begun in 1972 at the encouragement of the Congress, has made excellent progress in bringing minority institutions, faculties, and students into a great degree of participation in the biomedical research efforts of the country. In 1975 the program will award a total of 71 grants to 75 institutions, which will benefit approximately 350 faculty members and 1,000 undergraduate, graduate, and postdoctoral student participants. One of the most important features of these awards is the opportunity they provide to the students of these institutions to be exposed to biomedical research through involvement in laboratory procedures, attendance at scientific seminars and conferences, and personally presenting the results of their research at national meetings. We are already seeing in-

dications that students participating in MBS supported projects and programs are entering graduate schools and other health professional schools in greater numbers. We are extremely pleased with the progress experienced to date and fully expect these institutions to improve their scientific activities to the level where they will become more competitive within the categorical programs of the NIH over the next several years.

GENERAL RESEARCH SUPPORT

The narrative justification before you requests no funds for the general research support grant (GRSG) program in fiscal year 1976. This was based on the assessment that the primary objectives of the program had been attained and that, in view of the fiscal situation, the research needs of the Nation could better be served by the continued substantial support of the regular categorical research grant effort.

BUDGET

In conclusion, Mr. Chairman, the budget request for the Division of Research Resources for 1976 is $81,058,000. I shall be pleased to answer any questions and supply additional information desired for the record.

DIVISION OF RESEARCH RESOURCE MISSION

Mr. FLOOD. Doctor, in your opening statement you said you had established for your program a contemporary objective of meeting the research resource needs of NIH and of assuring the availability of those resources that are essential for the effective conduct of biomedical research.

That certainly sounds like you have identified a mighty important role for your organization.

Dr. BOWERY. We feel that is true, sir.

BUDGET REQUEST

Mr. FLOOD. Having said all that, suppose you tell us what the impact will be on your program if we approve this $47 million budget reduction? How do you add that up?

Dr. BOWERY. The funds included in the 1976 budget request will fund only continuing awards. These include competing as well as noncompeting continuations, since the Division funds centers and resources which have broad objectives, are for long-range purposes, and fiscal requirements that tend to be continuing.

This does not include any funds for a continuation of the general research support program, but we feel we can maintain a fairly stable continuation of our existing programs with the exception of the general research support program.

Mr. FLOOD. You hope?

Dr. BOWERY. Yes.

Mr. FLOOD. That is about all.

How much of this reduction is for your general research support grants?

Dr. BOWERY. Of the approximately $47 million, $43 million is for the reduction and elimination of the general research support program.

Mr. FLOOD. That is quite a slice.

Dr. BOWERY. Of the remaining $4 million, there is approximately a $2.6 million reduction in the laboratory animal sciences and primate research program and about a $1 million reduction in the clinical research programs.

GENERAL RESEARCH SUPPORT

Mr. FLOOD. In giving us this new objective for this program which you identified here in your opening statement, what part would this general research support play in meeting this objective if we restore the funding for these GRS grants? What part would they play?

Dr. BOWERY. The key role of the general research support program is to allow institutions flexibility to make adjustments in the conduct of the NIH research mission as certain emergencies or new opportunities arise and allow them the ability to make these onsite judgments rapidly. As they are trying to fine tune their programs to the categorical emphasis and direction of the NIH categorical institutes they will be able to do this in a much faster way and it also allows them discretion as to where they would like to place their funds to balance the various programs that are impacting upon their institution.

NEW GENERAL RESEARCH SUPPORT GUIDELINES

Mr. FLOOD. Last year the committee directed you to reconsider this formula for the guidelines under which these general research support grants were awarded, if you recall that, and report back to the committee prior to these hearings for the 1976 budget.

Dr. BOWERY. Yes, sir.

Mr. FLOOD. So we received the report just last week, under the wire. Would you care to summarize for the committee some of the recommendations in that report?

Dr. BOWERY. The objectives of the proposed biomedical research support grant program and its companion biomedical research development award program are essentially the same as the previous program.

Mr. FLOOD. Are you telling us now about what is in the report?

Dr. BOWERY. Yes, sir, I am summarizing the essence of the report, that the objectives are basically the same—to allow institutions to exercise onsite judgment, quick response to emerging opportunities and unpredictable needs in the institution, encourage innovation, and provide for pilot studies.

The changes are that the new programs provide for a common eligibility threshold, that is, each institution has to have $200,000 worth of active Public Health Service-supported research going on. A common allocation formula requires a more visible and productive internal advisory system within the institution to make judgment on the internal distribution of the funds and puts some restriction on the use of the funds for repetitive use in the area of salary support. The revision includes the companion, the Biomedical Research Developmental Award program for institutions who do not meet the basic criteria of $200,000 worth of active Public Health Service-supported research. Both of these programs include the opportunity for the program staff and its advisers to conduct onsite visits to monitor how these funds are being used.

Mr. FLOOD. Which of the institutions would benefit most by these revised guidelines?

Dr. BOWERY. There would be a shift of funds due to the common eligibility threshold and the common allocation formula.

Mr. FLOOD. I know that. Which institutions?

Dr. BOWERY. They would be the graduate school components of universities that do not have health professional schools.

Mr. FLOOD. It would be the smaller and the less wealthy institutions, wouldn't it?

Dr. BOWERY. Certainly with the addition of the companion, Biomedical Research Developmental Award program, the so-called smaller or less involved institutions would be given an opportunity to develop programs in biomedical research, which was not the case of the former general research support program.

Mr. FLOOD. Isn't there a need among all of these research institutions, especially the smaller research institutions, to have some kind of a degree of flexibility, for instance, to meet emerging opportunities—we were talking about it before—to provide for pilot studies, and to support this young scientist, a fellow who hasn't made a name for himself yet and who has difficulty, therefore, getting money to continue his research? Wouldn't that be about where you are?

Dr. BOWERY. That would continue to be a basic objective of the new program as it was the basic objective of the former program.

Mr. FLOOD. About these revised guidelines, did you talk that over with these institutions who have already received support under the general research support program already, and I suppose you have. If you have, what was their reaction to your revised guidelines?

Dr. BOWERY. The guidelines were developed both with involvement of the general research support program advisory committee, and the National Advisory Research Resources Council. Some 2,000 copies of the draft was sent into the field. We received 205 responses. In most cases they were very supportive of the new program. There were some replies that indicated there should be more money put into the Biomedical Research Developmental Award program. Some institutions that were very deeply involved in research, were concerned that too much would flow one direction versus the other. But in general these 205 responses were positively supportive of the change.

Mr. FLOOD. Will you supply for the record a copy of that GRS grant support. The report on that? We would like a report and also a list of the institutions who have received that GRS support in 1975.

[The information follows:]

3778 (A)

GENERAL RESEARCH SUPPORT GRANT
AND
BIOMEDICAL SCIENCES SUPPORT GRANT
PROGRAMS

OF
THE NATIONAL INSTITUTES OF HEALTH

A Report Requested
by
House of Representatives Report No. 93-1140, pages 45-46
and
Senate Report No. 93-1146, page 67

Prepared
by
Department of Health, Education, and Welfare
National Institutes of Health
Division of Research Resources

INTRODUCTION

The General Research Support Grant Program was authorized by P.L. 86-798, which was approved September 15, 1960. The first awards were made in FY 1962. Recipients of General Research Support Grants are medical and other health professional schools, hospitals, and other non-academic research institutions. In 1966, the companion Biomedical Sciences Support Grant Program was initiated. This program is conceptually identical to the General Research Support Grant Program, but provides funds to academic institutions other than health professional schools.

Previous evaluations led to major restructuring of the General Research Support Grant Program in 1968. This restructuring resulted in: the requirement that all participating institutions would satisfy the minimum entitlement levels; elimination of an automatic base grant of $25,000 for health professional schools; establishment of allowable NIH and NIMH grants as the entitlement base; and adoption of a new formula. During 1974, the Division of Research Resources program staff, with the assistance of the General Research Support Program Advisory Committee, the National Advisory Research Resources Council, and staff of the Office of the Director of NIH, conducted an assessment of grantee practices and accomplishments. This study continued with the development of proposed program modifications that are designed to promote the strengths of the program and to restrict or prohibit practices that may have a potential for abuse or be of low priority. Draft proposals were submitted to present and potential general research support grantees and other interested parties for comment. The DHEW and NIH policy continues to be that General Research Support is of relatively lower priority among the Agency's research programs for the following reasons:

A major purpose of the General Research Support Program--to build institutional biomedical research capabilities--has been largely accomplished.

The larger and relatively more wealthy universities tend to receive the larger dollar awards according to the formula by which the grants are distributed.

Regular NIH research project grants--based on competition for funds and peer group scientific review--are seen as a superior mechanism for the distribution of available biomedical research funds.

However, if Congress appropriates funds for the General Research Support Program in 1976, it is planned to improve the program in accordance with the proposals described in this report. As a result

of the study, two programs are proposed: a Biomedical Research Support Grant program, which would combine and modify the existing General Research Support Grant and Biomedical Sciences Support Grant Programs; and a Biomedical Research Development Grant program, which would support the development of research capability in small and new or developing institutions where the national biomedical research effort and the needs of NIH would be best served.

If these general proposals are accepted, specific guidelines will be developed for implementation.

BIOMEDICAL RESEARCH SUPPORT GRANT
(Currently General Research Support Grant and
Biomedical Sciences Support Grant Programs)

The General Research Support Grant (GRSG) and Biomedical Sciences Support Grant (BSSG) Programs will be combined as the Biomedical Research Support Grant (BRSG) Program.

OBJECTIVES

The general program objective will be to strengthen, to balance, and to stabilize Public Health Service supported biomedical and behavioral research programs. The proposed program will provide flexible institutional funds on a formula basis to non-Federal public and non-profit private health professional schools, universities, hospitals, research organizations and other institutions actively engaged in biomedical and behavioral research. These funds are to complement and to enhance the effectiveness and efficiency of biomedical and behavioral research in those institutions. The most distinguishing feature of the proposed program is the opportunity provided for grantee institutions to exercise on-site judgment regarding emphasis, specific direction, and content of activities supported, thus enabling the institution to respond quickly and effectively to emerging opportunities and unpredictable requirements, to enhance creativity, to encourage innovation, to provide for pilot studies, and to improve research resources, both physical and human.

This program thus recognizes the need to share resources and to respond to opportunities that develop during the course of active, diverse biomedical and behavioral research programs and to contribute to the stability of the national research effort.

ELIGIBILITY

Institutions that may apply for Biomedical Research Support Grants are limited to the following: health professional schools, non-Federal hospitals (whether or not a component of a university); state and municipal health agencies; academic institutions exclusive of health professional components; and non-academic non-profit research organizations. For the purposes of the BRSG program, each health professional school -- e.g., a school of dentistry, medicine, nursing, osteopathy, pharmacy, public health, or veterinary medicine -- is considered an "institution" even though it may be a component of a university.

Grantee institutions must be located in a State, the District of Columbia, Puerto Rico, the U. S. Virgin Islands, the Canal Zone, Guam, American Samoa, or the Trust Territory of the Pacific Islands.

Grantee institutions must have received at least $200,000 (including direct and indirect costs) in allowable Public Health Service biomedical and behavioral research grants for budget periods with beginning dates that fall within the latest complete Federal fiscal year.

The PHS Biomedical and Behavioral research grants allowable for eligibility and award computation purposes are those that fall into the following categories:

Code	Title
M 01	General Clinical Research Centers Program
P 01	Research Program Project Grants
P 02	Categorical Clinical Research Centers
P 06	Animal Resources
P 07	Biotechnology Resources
P 10	Environmental Health Centers
P 11	Pharmacology-Toxicology Centers
P 13	Dental Research Institute Program
P 15	Outpatient Clinical Research Program
P 17	Specialized Centers of Research
P 18	Sickle Cell Centers
R 01	Project Grants
R 02	Nursing Grants
R 03	Small Grants
R 10	Cooperative Clinical Research, Chemotherapy and Psychopharmacology Research Grants
R 12	Mental Health Special Grants
R 21	Exploratory Grants
R 22	U.S. - Japan Cooperative Medical Science Program
R 23	Special Research Award Program
R 24	Resource-Related Research Projects - Biotechnology Resources
R 26	National Targeted Projects
R 28	Resource-Related Projects - General Clinical Research Centers
S 06	Minority Biomedical Support

Review of applications will also consider the degree of diversity, complexity, and breadth of the institution's total biomedical research, based on factors such as the number and size of grants awarded to support that research, the numbers of granting agencies and awarding units, and the number of disciplines and fields represented.

LEVEL OF FUNDING

Of the funds appropriated and apportioned for this program, at least 90 percent will be awarded to successful applicants. Up to 10 percent will be designated for a companion Biomedical Research Development Program (vide infra).

COMPUTATION OF AWARD

Awards will be computed according to the following formula as applied to the allowable PHS biomedical and behavioral research project grants awarded to each applicant institution during the latest completed Federal fiscal year and adjusted by a uniform factor (prorated) to the funds available for the program. After proration, a maximum of $300,000 will be imposed on all awards. No minimum award level will be established.

Formula

Percentage Applied	Amount of Allowable PHS Biomedical & Behavioral Research Grant Support
15% of	the first $500,000 plus
10% of	$500,001 through $2,000,000, plus
5% of	$2,000,001 through $6,000,000
0% of	$6,000,001 and over

The maximum credit permitted for any one allowable PHS biomedical or behavioral research grant to which the formula is applied will be $500,000.

EMPHASIS FOR USAGE OF FUNDS

Grants from this program are intended to support primarily those biomedical and behavioral research activities not readily or normally supported by PHS categorical research grant programs. Examples are:

Pilot projects

Initial investigations in new fields and in fields new to the investigator

Unanticipated opportunities and requirements

New and more effective patterns of use of resources within and without the grantee institution

Central shared resources

Enhancement of investigator's biomedical research skills

Expansion of research capabilities through improved research opportunities for minorities and women

Animal welfare improvement

NEW REQUIREMENTS

Each grantee will be required to establish intra-institutional mechanisms acceptable to the National Institutes of Health:

to assure broadly-based review for advice on the use of the grant funds, with input from both scientific and administrative personnel of the grantee institution,

to disseminate information about the availability of the Biomedical Research Support Grant funds and the results achieved through use of the funds, and

to assure adequate programmatic and fiscal accountability.

Support of research salaries of tenured faculty will be permitted only on a short-term basis provided it can be justified. Such support to any one person may not exceed a cumulative total of six months in any two consecutive grant years except with prior approval by the National Institutes of Health. In the event of institution-wide salary increases, the prior approval requirement will be waived for those increases in the salaries supported from PHS grants allowable in the computation of the Biomedical Research Support Grant award, but only until the continuation, renewal, or termination of those PHS grants, whichever occurs first.

Supplementation of ongoing funded PHS research project grants is permitted only for unexpected or emergency needs.

Alterations and renovations of research facilities may be charged to the grant not to exceed 20 percent of the BRSG award for the current year, or $40,000, whichever amount is smaller. Carryover of this authority may be allowed with justification for up to one year, subject to prior approval by the National Institutes of Health.

COSTS NOT ALLOWED

The Public Health Service Grants Policy Statement, DHEW Publication No. (OS) 74-50,000 July 1, 1974, describes costs that are normally not allowed. In addition, the following costs will not be allowed under a Biomedical Research Support Grant:

Indirect costs.

Construction, other than alterations and renovations.

Broad institutional planning activities not directly related to the conduct of research.

Travel, other than that solely related to biomedical and behavioral research. Travel to seek grant support and for grant administrative purposes will not be permitted.

Support for biomedical and behavioral research grant projects disapproved by PHS National Advisory Councils.

Training. The National Research Service Act of 1974 prohibits support of training under the General Research Support Authority. Stipends will not be permitted. Grant funds may be used to pay salaries of students employed in biomedical and behavioral research.

Libraries. Refer to the Public Health Service Grants Policy Statement (page 12) for allowable costs of books and periodicals.

SITE VISITS

Each year site visits will be made to a sample of grantee institutions, representing all categories of institutions, and to any institution where NIH staff has identified a need for additional information concerning management of the grant and its accomplishments. Purposes for the visits include continuing assessment of program goals and policies, improvement in grantee management and correction of deficiencies, enhancement of program effectiveness, and confirmation of progress reports.

BIOMEDICAL RESEARCH DEVELOPMENT GRANT

A Biomedical Research Development Grant (BRDG) program is proposed as a companion program to the Biomedical Research Support Grant (BRSG) Program to assist eligible institutions to establish specific capabilities for the conduct of biomedical and behavioral research.

OBJECTIVES

The purpose of the Biomedical Research Development Grant program will be to enhance the achievement of the Federal commitment to discovery of new knowledge necessary for better health through research contributions from a broader array of institutions. The program is intended for those institutions that currently have limited involvement in biomedical and behavioral research, but possess the necessary potential and can justify such research advancement in terms of the national interest and the NIH mission.

ELIGIBILITY

Eligible institutions will be those which receive less than $200,000 of direct and indirect costs annually in PHS biomedical and behavioral research grant support as required for the proposed BRSG Program.

TYPE OF AWARD

Biomedical Research Development Grants will be awarded on the basis of detailed applications that describe institutional objectives for development of biomedical and behavioral research capability, existing strengths and weaknesses, and plans to achieve the objectives.

Applications may be submitted for up to three years of support in amounts averaging up to $100,000 per year. Awards may be renewable, but total support to any institution may not exceed six years in duration.

LEVEL OF FUNDING

Up to 10 percent of the funds appropriated and apportioned each year for the Biomedical Research Support Grant Program (formerly the General Research Support Grant and Biomedical Sciences Support Grant Programs), will be designated for support of the Biomedical Research Development Grant program.

REVIEW OF APPLICATIONS

Applications for new and competing renewal applications will be reviewed in national competition three times each year. Scientific

and technical merit will be evaluated by an initial peer review group, and the National Advisory Research Resources Council will act on approval of applications and advise on policy matters such as program priorities. Criteria for review of applications will include:

Commitment to biomedical research by the applicant institutions

Promise of effective biomedical research and advancement of the NIH mission

Meritorious and realistic objectives

Effective plans for achievement of objectives

Importance of the planned biomedical research capability to related national goals leading to improved health

Broader geographic representation in biomedical research

Examples of research development objectives are improvement and establishment of:

Scientific disciplinary areas of research

Interdepartmental research linkages

Multidisciplinary research teams

Central research resources

USES OF THE AWARD

Award funds may be used for direct costs that will develop the approved research capability. Examples are:

Recruitment of key investigators

Equipment of laboratories

Support of pilot research

Central shared resources

Establishment or strengthening of biomedical research in a discipline or field

COSTS NOT ALLOWED

The Public Health Service Grants Policy Statement, DHEW Publication No. (OS) 74-50,000 July 1, 1974, describes costs that are normally not allowed. In addition, the following costs will not be allowed under a Biomedical Research Development Grant:

Indirect Costs

Construction, other than alterations and renovations

Broad institutional planning activities not directly related to the conduct of research

Travel, other than that solely related to biomedical and behavioral research. Travel to seek grant support and for grant administrative purposes, is not permitted.

Support for biomedical and behavioral research grant projects disapproved by PHS National Advisory Councils.

Training. The National Research Service Act of 1974 prohibits support of training under the General Research Support Authority. Stipends will not be permitted. Grant funds may be used to pay salaries of students employed in biomedical and behavioral research.

Libraries. Refer to the Public Health Service Grants Policy Statement (page 12) for allowable costs of books and periodicals.

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GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
UNIV. OF ALABAMA, BIRMINGHAM-MEDICAL	255,345
UNIV. OF ARKANSAS, LITTLE ROCK-MED.	76,236
UNIVERSITY OF CALIFORNIA, IRVINE-MED	144,552
LOMA LINDA UNIVERSITY - MEDICAL	99,402
STANFORD UNIVERSITY, STANFORD - MED.	255,345
UNIVERSITY OF CALIFORNIA, L.A.-MED.	255,345
UNIVERSITY OF CALIFORNIA, S.F.-MED	255,345
UNIV. OF SOUTHERN CALIF., L.A.-MED.	241,496
UNIVERSITY OF COLORADO, DENVER -MED.	255,345
YALE UNIVERSITY, NEW HAVEN - MEDICAL	255,345
GEORGE WASHINGTON UNIVERSITY,DC-MED.	148,885
GEORGETOWN UNIVERSITY, D.C. -MEDICAL	169,259
HOWARD UNIVERSITY, D.C. - MEDICAL	161,250
UNIV. OF FLORIDA, GAINESVILLE - MED.	181,066
UNIVERSITY OF MIAMI - MEDICAL	255,345
EMORY UNIVERSITY, ATLANTA - MEDICAL	191,146
MEDICAL COLLEGE OF GEORGIA, AUGUSTA	143,098
CHICAGO MED SCHOOL/UNIV OF HLTH SCIS	53,853
UNIVERSITY OF CHICAGO-PRITZKER-MED.	255,345
LOYOLA U.,STRITCH SCH.MED.,MAYWOOD	118,027
UNIVERSITY OF ILLINOIS, CHICAGO-MED.	181,325
NORTHWESTERN UNIVERSITY, CHICAGO-MED	203,403
INDIANA UNIVERSITY, INDIANAPOLIS-MED	234,038
UNIVERSITY OF IOWA, IOWA CITY - MED.	255,345
UNIVERSITY OF KANSAS,KANSAS CITY-MED	172,879
UNIVERSITY OF KENTUCKY,LEXINGTON-MED	145,846
UNIVERSITY OF LOUISVILLE - MEDICAL	95,721
LOUISIANA ST. UNIV.,NEW ORLEANS-MED.	167,737
TULANE UNIVERSITY, NEW ORLEANS -MED.	190,299
JOHNS HOPKINS UNIVERSITY,BALTI.-MED.	255,345
UNIVERSITY OF MARYLAND, BALTI.-MED.	187,174
BOSTON UNIVERSITY-MEDICAL	255,345
HARVARD UNIVERSITY, BOSTON - MEDICAL	255,345
TUFTS UNIVERSITY, BOSTON - MEDICAL	196,474
UNIV. OF MICHIGAN, ANN ARBOR - MED.	255,345
WAYNE STATE UNIVERSITY, DETROIT-MED.	161,103
UNIV. OF MINNESOTA, MINNEAPOLIS-MED.	255,345
UNIV. OF MISSISSIPPI, JACKSON - MED.	163,029
UNIV. OF MISSOURI, COLUMBIA - MED.	163,106
SAINT LOUIS UNIVERSITY - MEDICAL	169,075
WASHINGTON UNIVERSITY, ST. LOUIS-MED	255,345
CREIGHTON UNIVERSITY, OMAHA-MEDICAL	61,247
UNIVERSITY OF NEBRASKA, OMAHA - MED.	60,524
DARTMOUTH COLLEGE, HANOVER - MEDICAL	173,943

GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
NJ COL OF MED & DENT, NEWARK - MED	138,737
ALBANY MED. COLLEGE OF UNION UNIV.	176,909
COLUMBIA UNIVERSITY, NEW YORK-MED.	255,345
CORNELL UNIVERSITY, NEW YORK-MEDICAL	249,883
YESHIVA U.,A.EINSTEIN COL.MED.,BRONX	255,345
NEW YORK MEDICAL COLLEGE, NEW YORK	183,434
NEW YORK UNIVERSITY, NEW YORK - MED.	255,345
STATE UNIV. OF NEW YORK, BUFFALO-MED	214,883
ST.U.OF N.Y.,DOWNSTATE,BROOKLYN-MED.	217,815
ST.U.OF N.Y.,UPSTATE, SYRACUSE-MED.	167,240
UNIVERSITY OF ROCHESTER - MEDICAL	255,345
WAKE FOREST U.BOWMAN GRAY SCH.OF MED	188,179
DUKE UNIVERSITY, DURHAM - MEDICAL	255,345
UNIV.OF NORTH CAROLINA,CHAP.HILL-MED	255,345
U.OF NORTH DAKOTA, GRAND FORKS -MED.	26,955
UNIVERSITY OF CINCINNATI - MEDICAL	191,241
OHIO STATE UNIVERSITY, COLUMBUS-MED.	163,652
CASE WESTERN RESERVE U.,CLEV. - MED.	255,345
UNIV. OF OKLAHOMA, OKLA. CITY - MED.	137,452
UNIVERSITY OF OREGON, PORTLAND -MED.	216,597
HAHNEMANN MED. COL. & HOSP., PHILA.	115,681
JEFFERSON MED COL OF T.J. UNIV,PHILA	170,080
UNIV. OF PENNSYLVANIA, PHILA.-MED.	255,345
UNIVERSITY OF PITTSBURGH - MEDICAL	219,030
TEMPLE UNIVERSITY, PHILADELPHIA-MED.	255,345
MEDICAL COLLEGE OF PENN., PHILA.	106,449
UNIV.OF PUERTO RICO, SAN JUAN-MED.	92,268
MED. U. OF SOUTH CAROLINA,CHARLESTON	163,838
UNIV.OF SOUTH DAKOTA,VERMILLION-MED.	29,293
MEHARRY MEDICAL COL., NASHVILLE-MED.	78,598
UNIVERSITY OF TENNESSEE,MEMPHIS-MED.	192,145
VANDERBILT UNIVERSITY,NASHVILLE-MED.	255,345
BAYLOR COLLEGE OF MEDICINE, HOUSTON	255,345
TEX.U OF.HLTH SCI CTR,SW MED SCH,DAL	255,345
UNIV. OF TEXAS, MED. BR., GALVESTON	200,364
UNIVERSITY OF UTAH, SALT LAKE - MED.	223,449
UNIV. OF VERMONT, BURLINGTON-MEDICAL	178,000
VA.COMM. U.,MED.COL.OF VA.,RICH-MED.	188,130
UNIV.OF VIRGINIA,CHARLOTTESVILLE-MED	205,402
UNIVERSITY OF WASHINGTON,SEATTLE-MED	255,345
WEST VIRGINIA UNIV., MORGANTOWN-MED.	84,652
MEDICAL COLLEGE OF WISCONSIN, INC.	178,838
UNIVERSITY OF WISCONSIN,MADISON-MED.	255,345
RUTGERS, STATE UNIVERSITY,PISCAT-MED	132,915

GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
UNIV. OF NEW MEXICO, ALBUQUERQUE-MED	205,235
UNIVERSITY OF HAWAII, HONOLULU -MED.	151,036
MT SINAI SCHL OF MED.CITY UNIV OF NY	255,345
U. OF TEXAS MED. SCH., SAN ANTONIO	146,292
MICHIGAN STATE UNIV., E.LANSING-MED.	137,903
BROWN UNIVERSITY, PROVIDENCE - MED.	97,911
UNIVERSITY OF CALIFORNIA, S.D.-MED	255,345
UNIVERSITY OF ARIZONA, TUCSON - MED.	181,216
UNIVERSITY OF CONNECTICUT.FARM.-MED.	157,739
PENNSYLVANIA STATE UNIV.,HERSHEY-MED	188,186
UNIVERSITY OF CALIFORNIA, DAVIS-MED.	165,086
MEDICAL COLLEGE OF OHIO AT TOLEDO	40,196
UNIV. OF MASSACHUSETTS,WORCESTER-MED	105,623
STATE UNIV. OF NEW YORK,STONYBRK-MED	117,849
UNIV. OF TEXAS MED.SCH., HOUSTON	148,664
UNIVERSITY OF S. FLORIDA, TAMPA-MED.	43,167
EASTERN VIRGINIA MED. SCHOOL,NORFOLK	16,527
TEXAS TECH UNIV., LUBBOCK - MED.	35,584
UNIV. OF SOUTH ALABAMA, MOBILE-MED.	49,245
UNIV. OF ALABAMA, BIRMINGHAM-DENTAL	168,123
UNIVERSITY OF THE PACIFIC,S.F.-DEN.	29,622
UNIV. OF SOUTHERN CALIF., L.A.-DENT.	86,553
UNIVERSITY OF CALIFORNIA, L.A.-DENT	62,391
UNIVERSITY OF CALIFORNIA, S.F.-DENT	59,950
GEORGETOWN UNIVERSITY, D.C. - DENTAL	16,382
EMORY UNIVERSITY, ATLANTA - DENTAL	51,376
UNIVERSITY OF ILLINOIS, CHICAGO-DENT	27,965
NORTHWESTERN UNIVERSITY, CHICAGO-DEN	33,689
INDIANA UNIVERSITY, INDIANAPOLIS-DEN	20,279
UNIVERSITY OF IOWA, IOWA CITY-DENTAL	123,312
UNIVERSITY OF MARYLAND, BALTI.-DENT.	15,969
HARVARD UNIVERSITY, BOSTON - DENT.	100,865
TUFTS UNIVERSITY, BOSTON - DENTAL	19,620
UNIV. OF MICHIGAN, ANN ARBOR - DEN.	158,877
UNIV. OF MINNESOTA, MINNEAPOLIS-DEN.	74,968
UNIV. OF MISSOURI, KANSAS CITY-DEN.	14,528
STATE UNIV. OF NEW YORK, BUFFALO-DEN	60,793
COLUMBIA UNIVERSITY, NEW YORK-DENTAL	15,396
NEW YORK UNIVERSITY, NEW YORK-DENTAL	36,937
UNIV.OF NORTH CAROLINA,CHAP.HILL-DEN	146,266
CASE WESTERN RESERVE U.,CLEV.-DENTAL	29,841
UNIVERSITY OF OREGON, PORTLAND -DEN.	36,745
UNIV. OF PENNSYLVANIA, PHILA.-DENTAL	137,891
UNIVERSITY OF PITTSBURGH - DENTAL	39,714

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GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
MEHARRY MEDICAL COL., NASHVILLE-DEN.	15,477
UNIVERSITY OF WASHINGTON,SEATTLE-DEN	33,898
WEST VIRGINIA UNIV., MORGANTOWN-DEN.	21,921
UNIVERSITY OF CONNECTICUT,FARM.-DEN.	132,187
BOSTON UNIVERSITY-DENISTRY	31,114
LOUISIANA ST. UNIV.,NEW ORLEANS-DENT	25,759
VA.COMM. U.,MED.COL.OF VA.,RICH-DENT	39,835
UNIV. OF FLORIDA, GAINESVILLE - DEN.	18,221
MED UNIV OF SO CAROLINA,CHARLES.-DEN	17,431
MICHIGAN STATE UNIV, E LANSING-OSTEO	17,700
UNIVERSITY OF CALIFORNIA, S.F.-PHAR	97,065
STATE UNIV. OF NEW YORK, BUFFALO-PHA	79,253
UNIVERSITY OF PITTSBURGH - PHARMACY	20,168
UNIVERSITY OF WISCONSIN,MADISON-PHAR	60,584
UNIV. OF MICHIGAN, ANN ARBOR -PHARM.	68,310
UNIV. OF FLORIDA, GAINESVILLE-PHARM.	40,365
PURDUE UNIVERSITY, LAFAYETTE -PHARM.	71,984
UNIV. OF MISSISSIPPI, UNIV.-PHARM.	41,058
UNIVERSITY OF KANSAS, LAWRENCE-PHARM	31,307
OHIO STATE UNIVERSITY, COLUMBUS-PHAR	42,481
UNIV. OF MINNESOTA, MINNEAPOLIS-PHAR	45,765
VA.COMM. U.,MED.COL.OF VA.,RICH-PHAR	33,937
UNIVERSITY OF UTAH, SALT LAKE - PHAR	38,707
UNIV. OF CONNECTICUT,STORRS-PHARMACY	22,912
PHILA. COLLEGE OF PHARM. & SCI.,PHIL	16,003
UNIV OF NORTH CAROLINA,CHPL HL-PHARM	28,186
UNIV. OF MARYLAND, BALTIMORE-PHARM.	16,509
UNIVERSITY OF CALIFORNIA, S.F.-NURS.	61,460
YALE UNIVERSITY, NEW HAVEN - NURSING	29,908
WAYNE STATE UNIVERSITY, DETROIT-NURS	19,851
OHIO STATE UNIVERSITY, COLUMBUS-NURS	18,267
UNIVERSITY OF WASHINGTON, SEATTLE	34,871
UNIVERSITY OF CALIFORNIA, DAVIS-VET.	94,300
COLORADO ST. UNIV., FT. COLLINS-VET.	89,917
PURDUE UNIVERSITY, W. LAFAYETTE-VET.	34,971
UNIVERSITY OF ILLINOIS, URBANA -VET.	27,660
UNIV. OF MINNESOTA, ST. PAUL - VET.	17,517
N.Y.ST.VET.COL. AT CORNELL U.,ITHACA	91,487
OHIO STATE UNIVERSITY, COLUMBUS-VET.	36,482
UNIV. OF PENNSYLVANIA, PHILA. - VET.	160,191
WASHINGTON STATE UNIV., PULLMAN-VET.	56,931
IOWA STATE UNIVERSITY, AMES - VET.	27,311
OKLAHOMA ST. UNIV.,STILLWATER - VET.	35,579
TUSKEGEE INST., SCH. VET. MEDICINE	45,108

GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
UNIVERSITY OF GEORGIA, ATHENS - VET.	15,538
UNIV. OF MISSOURI, COLUMBIA - VET.	32,409
MICHIGAN STATE UNIV., E.LANSING-VET.	68,596
UNIVERSITY OF CALIFORNIA,BERKELEY-PH	106,216
UNIVERSITY OF CALIFORNIA, L.A.-P.H.	81,365
YALE UNIVERSITY, NEW HAVEN-PUB.HLTH.	110,796
TULANE UNIVERSITY, NEW ORLEANS -P.H.	24,474
JOHNS HOPKINS UNIVERSITY,BALTI.-P.H.	234,701
HARVARD UNIVERSITY, BOSTON -PUB.HLTH	234,565
UNIV. OF MICHIGAN, ANN ARBOR -P.H.	127,089
UNIV. OF MINNESOTA, MINNEAPOLIS-P.H.	27,629
COLUMBIA UNIVERSITY, NEW YORK-P.H.	131,074
UNIV.OF NORTH CAROLINA,CHAP.HILL-P.H	35,080
UNIVERSITY OF PITTSBURGH - PUB.HLTH.	70,335
UNIVERSITY OF WASHINGTON,SEATTLE-P.H	86,174
UNIVERSITY OF FLORIDA, GAINSVLLE	20,039
CHILDRENS HOSP. MED. CENTER, OAKLAND	39,295
CEDARS-SINAI MEDICAL CTR.,L.A.-HOSP.	121,429
CHILDRENS HOSPITAL OF LOS ANGELES	116,321
CITY OF HOPE NAT MED CTR,DUARTE-HOSP	147,319
MOUNT ZION HOSP. & MED. CENTER, S.F.	52,675
NATIONAL JEWISH HOSPITAL AT DENVER	106,417
CHILDRENS MEMORIAL HOSPITAL, CHICAGO	99,120
MICHAEL REESE HOSP.&MED.CTR.,CHICAGO	112,168
RUSH-PRES-ST LUKES MED CTR,CHIC-HOSP	137,906
SINAI HOSPITAL OF BALTIMORE, INC.	39,700
BETH ISRAEL HOSPITAL, BOSTON	126,528
CHILDRENS HOSP. MED. CTR., BOSTON	255,345
MCLEAN HOSPITAL, BELMONT	68,410
MASS. EYE AND EAR INFIRMARY, BOSTON	75,597
MASSACHUSETTS GENERAL HOSP., BOSTON	255,345
UNIVERSITY HOSPITAL, INC., BOSTON	160,662
PETER BENT BRIGHAM HOSPITAL, BOSTON	155,170
HENRY FORD HOSPITAL, DETROIT	42,987
JEWISH HOSPITAL OF ST. LOUIS	66,764
CHILDRENS HOSPITAL OF BUFFALO	80,195
HOSPITAL FOR SPECIAL SURGERY, N.Y.	85,565
L.I.JEWISH-HILLSIDE MED.CNTR.	83,386
MAIMONIDES MEDICAL CENTER, BROOKLYN	33,027
MARY IMOGENE BASSETT HOSP.,COOPERSTN	43,564
MONTEFIORE HOSP. & MED. CTR., BRONX	220,703
ST. LUKES HOSPITAL CENTER, NEW YORK	107,628
ST. VINCENTS HOSP.& MED.CTR. OF N.Y.	43,124
JEWISH HOSP. & MED. CTR. OF BROOKLYN	26,441

GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
ALBERT EINSTEIN MED. CENTER, PHILA.	63,598
CHILDRENS HOSPITAL OF PHILADELPHIA	138,357
CHILDRENS HOSPITAL OF PITTSBURGH	67,183
PHILADELPHIA GENERAL HOSPITAL	136,501
WILLS EYE HOSPITAL, PHILADELPHIA	47,459
U.TEXAS,MD ANDERSON HOSP&TUM,HOUSTON	255,345
KAISER FOUNDATION HOSPITALS, OAKLAND	54,228
CHILD.ASTHMA RES.INST.& HOSP.,DENVER	32,157
CHILDRENS HOSPITAL, CINCINNATI	140,916
U.OF TENN.MEM.RES.CTR.& HOSP.,KNOX.	78,911
BALTIMORE CITY HOSPITALS	54,476
BOSTON CITY HOSPITAL	112,037
MAGEE-WOMENS HOSPITAL, PITTSBURGH	32,529
ST. JOSEPHS HOSPITAL, PHOENIX	67,028
ST. ELIZABETH HOSPITAL, BRIGHTON	36,588
HOSP. FOR JOINT DIS. & MED.CTR.,N.Y.	39,657
PENNSYLVANIA HOSPITAL, PHILADELPHIA	54,519
NEW ENGLAND DEACONESS HOSP., BOSTON	28,198
MONTEFIORE HOSP.ASSOC.W.PA., PITTS.	41,833
GOOD SAMARITAN HOSP.& MED.CTR.,PORT.	25,396
NEW ENGLAND MED. CTR. HOSPS., BOSTON	200,230
PRESBY.-UNIV.OF PA. MED.CTR., PHILA.	71,758
ST. CHRISTOPHERS H.FOR CHILD.,PHILA.	51,252
EVANSTON HOSPITAL, ILLINOIS	29,931
SINAI HOSPITAL OF DETROIT	62,037
ST. LUKES HOSPITAL, CLEVELAND	22,878
ROSWELL PARK MEMORIAL INST., BUFFALO	255,345
N.Y. ST. PSYCHIATRIC INSTITUTE, N.Y.	107,034
ROCKLAND PSYCHIATRIC CTR, ORANGEBURG	57,534
CHILD.ORTHO.HOSP.& MED.CTR., SEATTLE	25,099
MT. SINAI HOSPITAL OF CLEVELAND	41,005
ST. VINCENT HOSPITAL, WORCESTER	49,202
MT. SINAI HOSP. OF GTR. MIAMI, INC.	29,464
ROOSEVELT HOSPITAL, NEW YORK	62,362
ROBERT B. BRIGHAM HOSPITAL, BOSTON	79,221
MERCY CATHOLIC MED.CTR.SE.PA.,DARBY3	16,330
ALLEGHENY GENERAL HOSPITAL, PITTS.	75,065
PUTNAM MEMORIAL HOSPITAL,BENNINGTON3	25,591
MEM.HOSP.FOR CANCER&ALLIED DIS.,NY.	184,785
U OF CALIF.LANGLEY PORTER NEURO INST	122,318
U OF CALIF.NEUROPSYCHIATRIC INST,L A	201,862
NEWARK BETH ISRAEL MEDICAL CENTER	15,856
ROGER WILLIAMS GEN. HOSP.,PROVIDENCE	117,630
CALIF.ST.DEPT.OF PUB.HLTH., BERKELEY	53,468

GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
DIV.HLTH.DEPT.HLTH&REHAB.SER.ST.FLA.	53,107
PRO. STAFF ASSOC. LAC/USC MED. CTR.	42,982
FORSYTH DENT.INF.FOR CHILDREN.BOSTON	124,109
PALO ALTO MEDICAL RESEARCH FDN.	53,973
SCRIPPS CLINIC AND RES.FDN.,LA JOLLA	240,489
RES. FDN. OF CHILDRENS HOSP. OF D.C.	75,494
MENNINGER FOUNDATION. TOPEKA	15,515
ALTON OCHSNER MED. FDN., NEW ORLEANS	36,800
SOUTHWEST FDN. FOR RES. & ED., S.A.	94,681
PACIFIC NORTHWEST RES. FDN., SEATTLE	43,694
STANFORD RESEARCH INST., MENLO PARK	143,339
HEKTOEN I. MED.RES.OF COOK CO.,CHIC.	48,804
BIO-RESEARCH INST., INC., CAMBRIDGE	43,999
SIDNEY FARBER CANCER CENTER. BOSTON	236,786
EYE RES INST OF RETINA FDN. BOSTON	110,932
WORCESTER FDN.EXPER.BIOL.,SHREWSBURY	171,626
MICHIGAN CANCER FOUNDATION. DETROIT	106,029
MAYO FOUNDATION. ROCHESTER. MINN.	255,345
PUBLIC HEALTH RESEARCH INST., N.Y.	132,644
FELS RESEARCH INST., YELLOW SPRINGS	51,476
OKLAHOMA MED.RES.FDN., OKLAHOMA CITY	94,128
INSTITUTE FOR CANCER RESEARCH,PHILA.	250,558
WISTAR INST. OF ANAT. & BIOL.,PHILA.	185,653
A.S.A. RANCHO L.AMIGOS HOSP., DOWNEY	83,040
JACKSON LABORATORY. BAR HARBOR	139,471
FRIENDS MED. SCI.RESEARCH CENTER,INC	53,699
MARINE BIOLOGICAL LAB., WOODS HOLE	17,950
EASTMAN DENTAL CENTER. ROCHESTER. NY	48,396
P.S.A. LAC HARBOR GEN HOSP. TORRANCE	173,487
MASS. MENTAL HEALTH RES.CORP.,BOSTON	29,934
INSTITUTE OF MEDICAL SCIENCES. S. F.	148,357
INSTITUTE FOR MED. RESEARCH. CAMDEN	60,030
ST. JUDE CHILDRENS RES.HOSP.,MEMPHIS	166,093
VA. MASON FDN.MED.ED.& RES., SEATTLE	45,962
SALK INST FOR BIOL STUDIES.SAN DIEGO	176,644
HASKINS LABORATORIES. INC.,NEW HAVEN	54,167
HOME FOR JEWISH AGED. PHILADELPHIA	25,717
OREGON RESEARCH INSTITUTE. EUGENE	103,623
AMER.INST.FOR RES.BEHAV.SCI., PITTS.	41,728
CANCER RESEARCH CENTER. COLUMBIA	64,330
NEW YORK BOTANICAL GARDEN. BRONX	24,660
CENTER FOR BLOOD RES. INC. BOSTON	44,093
TEXAS RES.INST.MENTAL SCI., HOUSTON	34,880
INST. FOR BEHAVORIAL RES., SIL. SPG.	55,266

GENERAL RESEARCH SUPPORT PROGRAM

GENERAL RESEARCH SUPPORT GRANT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
N.Y.ST.HLTH.D..DIV.LAB.&RES., ALBANY	118,924
GULF SOUTH RES.INST., NEW ORLEANS	33,575
JOSLIN DIABETES FDN., INC., BOSTON	101,179
CLEVELAND CLINIC FOUNDATION	128,643
BOYCE THOMPSON I.FOR PLANT RES.,N.Y.	22,223
NATIONAL BIOMEDICAL RESEARCH FDN.,DC	40,753
NEW YORK BLOOD CENTER, NEW YORK	165,207
AMER. DENTAL ASSOCIATION, CHICAGO	38,297
PAPANICOLAOU CANCER RESEARCH INST.	69,571
JOHN B.PIERCE FDN.CONN.INC.NEW HAVEN	69,802
MEDICAL RESEARCH FDN.OF OREGON.PORT.	205,378
TRUDEAU INSTITUTE.INC., SARANAC LAKE	65,626
N.Y.ST.RES.INST.NEURO.& DRUG ADD.,NY	26,732
THE RAND CORPORATION, SANTA MONICA	67,661
BOSTON BIOMEDICAL RESEARCH INST.INC.	127,842
MEDICAL FOUNDATION OF BUFFALO	71,133
COLD SPRING HARBOR LABORATORY, N.Y.	145,638
INST.FOR RES.IN SOC.BEHAV.,BERKELEY6	31,567
BATTELLE MEMORIAL INST COLUMBUS LAB6	72,514
EUNICE K.SHRIVER MENT.RETARD.WALTHAM	114,590
ASSOC.UNIV.INC.BROOK.NAT.LAB.,UPTON6	151,123
CHILD RES. CNTR. OF MICHIGAN,DETROIT	19,583
AMERICAN NATIONAL RED CROSS, D.C.60	38,587
CENTER FOR POLICY RESEARCH, INC,N.Y.	71,795
IIT RESEARCH INSTITUTE	47,452
OAK RIDGE ASSOCIATED UNIV.,OAK RIDGE	59,917
MNTL.HLTH.RES.UNIT NY.DEPT.MNTL.HYG.	23,474
FRED HUTCHINSON CANCER RES CTR,SEATL	139,056
MASONIC MED RES LAB, UTICA	26,054
MOUNT DESERT ISLAND BIO LAB, PITTS.	30,336
INST FOR MED RES OF SANTA CLARA CNTY	29,210
GORGAS MEM INST OF TROP&PREV MED,DC	37,573

BIOMEDICAL SCIENCES SUPPORT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
UNIVERSITY OF ALASKA, COLLEGE	33,518
UNIVERSITY OF ARIZONA, TUCSON	40,236
CALIF. INST. OF TECHNOLOGY, PASADENA	99,887
STANFORD UNIVERSITY, STANFORD	73,069
UNIVERSITY OF CALIFORNIA, BERKELEY	162,978
UNIVERSITY OF CALIFORNIA, DAVIS	76,288
UNIVERSITY OF CALIFORNIA, IRVINE	53,448
UNIVERSITY OF CALIFORNIA, L.A.	78,655
UNIVERSITY OF CALIFORNIA, RIVERSIDE	39,312
UNIVERSITY OF CALIFORNIA, SAN DIEGO	91,178
UNIV. OF SOUTHERN CALIF., L.A.	44,982
UNIVERSITY OF COLORADO, BOULDER	54,502
UNIVERSITY OF CONNECTICUT, STORRS	51,092
YALE UNIVERSITY, NEW HAVEN	65,814
UNIVERSITY OF DELAWARE, NEWARK	30,840
GEORGE WASHINGTON UNIVERSITY, D.C.	45,831
FLORIDA STATE UNIVERSITY,TALLAHASSEE	48,416
UNIVERSITY OF FLORIDA, GAINESVILLE	46,891
UNIVERSITY OF MIAMI, CORAL GABLES	28,069
EMORY UNIVERSITY, ATLANTA	49,827
GEORGIA INST. OF TECHNOLOGY, ATLANTA	37,197
UNIVERSITY OF GEORGIA, ATHENS	42,966
UNIVERSITY OF HAWAII, HONOLULU	50,006
ILLINOIS INSTITUTE OF TECH., CHICAGO	19,015
NORTHWESTERN UNIVERSITY, EVANSTON	64,791
UNIVERSITY OF CHICAGO	41,505
UNIVERSITY OF ILLINOIS, URBANA	84,142
INDIANA UNIVERSITY, BLOOMINGTON	59,511
PURDUE UNIVERSITY, LAFAYETTE	69,243
UNIVERSITY OF NOTRE DAME, NOTRE DAME	40,466
IOWA STATE UNIV. OF SCI.& TECH.,AMES	41,857
UNIVERSITY OF IOWA, IOWA CITY	35,260
KANSAS STATE UNIVERSITY, MANHATTAN	31,419
UNIVERSITY OF KANSAS, LAWRENCE	67,389
LOUISIANA STATE UNIV., BATON ROUGE	29,048
JOHNS HOPKINS UNIVERSITY, BALTIMORE	54,633
UNIVERSITY OF MARYLAND, COLLEGE PARK	36,251
BOSTON UNIVERSITY	34,981
BRANDEIS UNIVERSITY, WALTHAM	48,917
HARVARD UNIVERSITY, CAMBRIDGE	70,388
MASS. INST. OF TECH., CAMBRIDGE	165,151
UNIV. OF MASSACHUSETTS, AMHERST	50,841
MICHIGAN STATE UNIV., EAST LANSING	44,248
UNIV. OF MICHIGAN, ANN ARBOR	63,497
WAYNE STATE UNIVERSITY, DETROIT	40,248
UNIVERSITY OF MINNESOTA, MINNEAPOLIS	72,167
UNIVERSITY OF MISSOURI, COLUMBIA	32,405

BIOMEDICAL SCIENCES SUPPORT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
WASHINGTON UNIVERSITY, ST. LOUIS	63,017
UNIVERSITY OF NEBRASKA, LINCOLN	32,010
DARTMOUTH COLLEGE, HANOVER	19,729
PRINCETON UNIVERSITY	55,914
RUTGERS, STATE UNIVERSITY, NEW BRUNS	65,607
RUTGERS, STATE UNIVERSITY, NEWARK	38,230
COLUMBIA UNIVERSITY, NEW YORK	53,616
CORNELL UNIVERSITY, ITHACA	76,375
NEW YORK UNIVERSITY, NEW YORK	37,232
POLYTECHNIC INSTITUTE OF NEW YORK	20,585
QUEENS COLLEGE,CITY UNIV OF NY,FLUSH	28,382
ROCKEFELLER UNIVERSITY, NEW YORK	141,159
STATE UNIV. OF NEW YORK, BUFFALO	43,094
STATE UNIV. OF NEW YORK, STONY BROOK	45,113
SYRACUSE UNIVERSITY	44,365
UNIVERSITY OF ROCHESTER	39,865
DUKE UNIVERSITY, DURHAM	39,741
NORTH CAROLINA STATE UNIV., RALEIGH	40,993
UNIV.OF NORTH CAROLINA,CHAP.HILL	50,947
OHIO STATE UNIVERSITY, COLUMBUS	58,041
OKLA.ST.U.AGRI.& APPL.SCI.,STILLWTR.	22,844
UNIVERSITY OF OKLAHOMA, NORMAN	23,403
OREGON STATE UNIVERSITY, CORVALLIS	55,848
UNIVERSITY OF OREGON, EUGENE	47,299
CARNEGIE-MELLON UNIVERSITY, PITTS.	44,667
PENNSYLVANIA STATE UNIV., UNIV. PARK	55,325
UNIV. OF PENNSYLVANIA, PHILA.	72,094
UNIVERSITY OF PITTSBURGH	58,333
BROWN UNIVERSITY, PROVIDENCE	38,372
GEO. PEABODY COL. FOR TEACHERS,NASH.	37,339
UNIVERSITY OF TENNESSEE, KNOXVILLE	33,557
VANDERBILT UNIVERSITY, NASHVILLE	35,862
TEXAS A&M UNIV., COLLEGE STATION	32,376
UNIVERSITY OF TEXAS, AUSTIN	58,658
UNIVERSITY OF UTAH, SALT LAKE CITY	59,553
UTAH STATE UNIVERSITY, LOGAN	19,658
UNIV. OF VIRGINIA, CHARLOTTESVILLE	49,914
VIRGINIA POLYTECH. INST., BLACKSBURG	33,937
UNIVERSITY OF WASHINGTON, SEATTLE	109,458
WASHINGTON STATE UNIV., PULLMAN	33,114
UNIVERSITY OF WISCONSIN, MADISON	150,503
UNIVERSITY OF CALIFORNIA, SANTA BARB	43,133
RICE UNIVERSITY, HOUSTON	40,448
RENSSELAER POLYTECHNIC INST., TROY	32,117
WESLEYAN UNIVERSITY, MIDDLETOWN	28,071
HUNTER COLLEGE OF CITY UNIV OF NY	29,815
AMHERST COLLEGE, AMHERST	25,934

BIOMEDICAL SCIENCES SUPPORT AWARDS

FY 1975 AWARDS

NAME OF INSTITUTION	TOTAL AWARDED
ARIZONA STATE UNIVERSITY, TEMPE	33,568
CASE WESTERN RESERVE UNIV.,CLEVELAND	54,324
UNIVERSITY OF KENTUCKY, LEXINGTON	33,542
TEMPLE UNIVERSITY, PHILADELPHIA	37,727
HOWARD UNIVERSITY, D.C.	36,913
SOUTHERN ILLINOIS UNIV., CARBONDALE	19,426
BROOKLYN COLLEGE OF CITY UNIV OF NY	20,641
STATE UNIVERSITY OF NEW YORK, ALBANY	40,476
CATHOLIC UNIVERSITY OF AMERICA, D.C.	24,117
YESHIVA UNIVERSITY, N. Y.	27,350
U.OF VERMONT ST.AGRI.COL.,BURLINGTON	34,996
CITY UNIVERSITY OF NEW YORK	37,234
COLORADO STATE UNIVERSITY,FT.COLLINS	35,903
OAKLAND UNIVERSITY	26,966
UNIVERSITY OF TEXAS, DALLAS	26,463
UNIVERSITY OF MONTANA, MISSOULA	23,664
UNIVERSITY OF CALIFORNIA, SANTA CRUZ	20,965
GEORGETOWN UNIVERSITY, D.C.	20,390
UNIVERSITY OF DENVER	33,598
HAVERFORD COLLEGE	24,234
NORTHEASTERN UNIVERSITY, BOSTON	21,367
UNIVERSITY OF HOUSTON	28,686
U OF TEX HLTH SCI CTR.GRAD SCH.HOUST	43,794
SUNY, BINGHAMTON	21,123
FORDHAM UNIVERSITY, BRONX	33,397
UNIVERSITY OF ALABAMA, UNIVERSITY	22,764
CALIFORNIA STATE UNIVERSITY, L.A.	23,145

Dr. BOWERY. There were 461 institutions located in 47 of the 50 States that received support in 1975.

AVAILABILITY OF NONHUMAN PRIMATES

Mr. FLOOD. We have heard a great deal here about this decreasing supply of primates, due to importation restrictions of course. How will these restrictions affect the extramural research programs at NIH?

Dr. BOWERY. Currently our usage of nonhuman primates, particularly the Rhesus monkey, which is the primate most commonly used in NIH's extramural programs amounts to approximately 6,000 per year.

Mr. FLOOD. Is that a lot?

Dr. BOWERY. The total U.S. usage is around 46,000, not including that of industry. It is a fair percentage of the total research usage. We have this past year awarded 4 contracts that will, in about 5 years, produce approximately 40 percent of the total requirements.

We are hoping that with possible shifting to other animal species and change in the utilization of primates in the research program, we might be able to come closer to meet that 6,000 goal.

Mr. FLOOD. If a significant proportion of this biomedical research which now involves human subjects must be transferred to animal models, such as primates, what would be your estimate of the number of primates that you are going to need in the next 5 to 10 years?

Dr. BOWERY. Although a national commission is taking a look at the impact of practices involving the use of human subjects for research, we really haven't had enough time to make an estimate of the number of primates that would be required. We feel in order to double our domestic breeding capacity over the next 5 years, from the approximate 2,300 animals which we are shooting for now, it will take an additional $4 to $5 million.

Mr. FLOOD. You have no estimate now. Do you think you can give us an estimate before this record is printed up of the number of primates, under all these circumstances in this shift, that you are going to need, say in the next 5 to 10 years, an intelligent estimate?

Dr. BROWERY. We can make an estimate.

Mr. FLOOD. Do the best you can.

Dr. BROWERY. Yes, sir.

[The information follows:]

The United States uses approximately 46,000 primates of a number of species yearly for biomedical research purposes. It is anticipated that the number used over the next 5 years will vary from 46,000–50,000 annually, assuming continuation of the current rate of usage. If however, it is no longer possible to use human subjects in research it will be necessary to use the nonhuman primate in several areas. This would increase the number of primates required for research proposed by an estimated 15 percent or approximately 7,200 primates per year.

Mr. FLOOD. How will your budget request alleviate the shortage of primates needed for research in that budget you are talking about?

Dr. BOWERY. The proposed budget would cause us to reduce the number of contracts probably from five to three, and thus reduce the number of animals we would anticipate being able to deliver from approximately 2,300 down to 1,900.

Mr. FLOOD. What leadtime, and funding, of course, would be required to double our current supply of primates?

Dr. BOWERY. I think the leadtime is the 4 to 5 years and at a cost of $4 to $5 million.

CLINICAL RESEARCH

Mr. FLOOD. You said that the clinical research program provides about 80 percent of the research beds supported extramurally at NIH. Who supports the other 20 percent?

Dr. BOWERY. Basically it is made up of support from the Cancer Institute, the Heart Institute, and the Arthritis Institute, with the remaining institutes picking up a very small percenage.

Mr. FLOOD. Take a look at your justifications on page 239 for the clinical research program. There you show the number of outpatient visits increasing, going up, the number of inpatient hospital days decreasing, going down.

Do you see that trend continuing, over, say, the next 3 to 5 years? By that I mean do you see the demand for the utilization of inpatient hospital beds decreasing?

Dr. BOWERY. I don't think the demand for inpatient beds will tend to decrease. This decrease is basically because of fiscal constraints.

Mr. FLOOD. Provide this for us in the record—give us a list of the clinical research centers and the bed occupancy rate of each center.

Dr. BOWERY. All right.

[The information follows:]

Bed Occupancy Rates in General Clinical Research Centers

Hospital bed occupancy rates are calculated as patient days per available bed days. Hospitals never achieve 100% occupancy over an extended period, because time is lost in the dovetailing of discharges and admissions, in scheduling problems with the patient care staff, and in the restrictions of beds to special purposes (e.g., obstetrics, newborns, intensive care, etc.). The DHEW 1971 Master Facility Inventory Survey, published in 1974, shows that for all general hospitals in this country, the average occupancy rate was 77%, while for general hospitals of less than 25 beds, it was 52%. In a sample of 999 general and community hospitals studied in 1973 and the first six months of 1974 by the Journal of the American Hospital Association, occupancy was 75%. The most recent average inpatient occupancy on the 84 GCRCs was 74%, only two of which are larger than 25 beds. However, for reasons to be discussed below, bed occupancy rates do not have the same significance for research wards as for a general hospital.

The optimum occupancy rate is different on research and general care wards because they differ in purpose, size, structure, and patient population. General hospitals admit patients for their medically indicated needs, and they have a large number of beds at their disposal. During periods of high demand for beds they can defer elective admissions without jeopardizing the patients' health. Research wards, on the other hand, are small enclaves which admit patients on the basis of their significance as research subjects and their suitability for study, irrespective of their general health status, and they have a limited number of beds. Patients whose admission to a research unit must be deferred because space is unavailable may be lost to useful scientific inquiry. It is therefore better to maintain an appropriate capacity of Center beds than to loose irreplaceable research opportunities. However, because Centers are usually one-third or less the size of nonresearch wards in the same hospital, a single bed held open for an anticipated patient has a larger percentage effect on the occupancy rate of the research ward.

Occupancy rates on Centers are affected by scheduling factors which are not important on nonresearch wards. Research patients are usually not acutely ill, and their admission is arranged for the mutal convenience of the patients, the investigators, and the supporting laboratory staff. Hospitalizations for research are often difficult to arrange while school is in session, and during Christmas or other holidays. Weekends are often useless for research purposes because laboratory services are not available. Patients admitted for necessary care, on the other hand, must remain hospitalized even during those times when diagnostic studies are unavailable. Also, research protocols commonly demand long uninterrupted periods of patient observations, so that an interval which may be available between the discharge of one long-term patient and the admission of another is too short to be utilized. Research subjects occasionally change their minds about serving as experimental patients, or after admission may be found to be unsuitable for study. In these situations, it may be difficult to reschedule another patient on short notice. There has been an increasing number of occasions when fiscal constraints have forced Program Directors to limit research unit occupancy below capacity, in order to conserve sufficient funds for adequate nursing care or core laboratory support.

Moreover, although the net occupancy rate is a reasonable measure of the patient care delivered on a nonresearch ward, it is not an accurate picture of the true level of investigative activity on a research unit. This is because much of the clinical research performed on these units does not result in the recording of a patient day. A bed recorded as empty may actually have been used for most of the day by a patient on a research protocol because the day of discharge is generally not counted for census purposes. Also, many investigations on Centers involve studies of outpatients who occupy a bed, sometimes for as long as six or eight hours, or a bed may be utilized for brief periods of examination and treatment of several outpatients. Outpatients are included in the following table in order to reflect their utilization of space, demands on staff and the cost of ancillary service at a ratio of three outpatient visit to one inpatient day. As the number of outpatients increases a different ratio may become appropriate.

Occupancy for the years 1971 through 1973 was calculated on a 365 day basis which has wide acceptance as the basis for calculating occupancy of American Hospitals. In order to more accurately reflect the time available for investigative activities occupancy for 1974 was recalculated on a "days open" basis where this information was available. Thus in centers where there were clearly identified blocks of time when the center was closed for vacations, holidays, moving or other reasons occupancy was recalculated on the number of days open rather than the more usual 365 day basis. This method resulted in a slightly higher occupancy for the overall program of approximately 3%. This brings the average occupancy rate for the Centers to 74%, excluding an allowance for outpatients, which is in line with the national occupancy rate of 75% for large general hospitals. This also is considerably above the occupancy rate of 52% for hospitals with less than 25 beds. This "day open" method has considerable merit in that it more accurately reflects the time available for investigation on these specialized research units and will be used on a program wide basis in the future.

In summary, certain special problems of medical research make it inappropriate to compare directly the occupancy rates on research wards to those on wards devoted to patient care. The appropriate occupancy for each unit is necessarily influenced by the size of the unit, the types of research studies underway, alternatives to utilization of space and staff and the need to preserve the research direction of the unit.

Clinical Research Centers
Beds & Occupancy

	FY 1971		FY 1972		FY 1973		FY 1974 3/		FY 1975 6/
	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds Funded
Duke University	17	84.2	17	88.8	17	81.1	17	90.9	15
Harvard University	18	96.5	24	76.7	16	96.2	16	109.3 4/	18
University of Alabama	10	73.8	10	78.9	10	82.3	10	90.1	10
Ohio State University	10	50.8	10	63.0	10	70.7	10	61.5	10
Johns Hopkins University	16	92.6	21	67.3	21	67.8	21	69.5	16
Washington University	33	84.2	33	79.1	33	72.6	33	70.0	33
University of Washington	16	62.5	16	68.2	16	85.9	16	47.9 5/	12
Emory University	10	89.0	10	102.8	10	100.9	12	92.5	12
University of Pennsylvania	10	63.3	10	61.1	10	60.2	10	62.0	10
University of Michigan	20	85.1	20	81.8	20	75.7	20	71.1	15
University of Southern Calif.	10	91.9	10	90.1	10	81.3	10	82.8	10
University of Rochester	8	89.1	8	87.6	8	94.6	8	94.7	8
University of North Carolina	12	60.6	12	72.3	12	62.9	12	62.2	12
Cornell University	24	71.6	24	69.3	24	79.3	12	173.2 4/	12
Northwestern University	9	90.5	8	99.4	8	102.4	8	86.3	8
University of Arkansas	8	108.5	8	138.9	8	143.1 1/			
Albert Einstein	12	49.2 5/	12	39.6 5/	12	54.9	12	78.0	8
University of Colorado	18	83.8	18	91.3	18	99.3	18	99.0	18
Johns Hopkins University	12	53.3	12	61.4	10	52.6	8	56.1	8
Montefiore Hospital	15	76.5	16	64.0	16	60.6	16	61.9	16
New England Medical Center Hosp.	14	55.3	14	71.8	14	58.5	14	55.3	10
University of Chicago	10	86.8	10	86.8	12	59.1	10	58.3	10
University of Pittsburgh	14	48.2 5/	14	34.5 5/	10	43.1 5/	10	60.2	10
Medical College of Wisconsin	12	70.2	10	77.6	10	70.0	10	75.3	7
University of Iowa	10	122.4	14	105.6	12	113.7	12	134.6 4/	12
Georgetown University	12	68.2	16	62.6	16	75.6	10	125.7 4/	6
University of Oklahoma	10	75.3	10	56.2	10	71.4	8	93.9	8
University of Puerto Rico	12	62.4	12	66.2	12	55.9	12	64.5	12
University of Utah	15	51.2	15	70.9	15	68.2	15	67.0	15
Virginia Commonwealth Univ.	10	54.5	10	57.4	10	68.6	10	51.5	7
University of Kansas	8	79.7	6	106.4 1/					

	FY 1971		FY 1972		FY 1973		FY 1974 3/		FY 1975 6/
	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds Funded
University of Cincinnati	6	106.6	6	132.8	6	92.2	6	77.8	6
University of Colorado	6	84.7	6	88.6	6	85.0	6	97.2	6
Stanford University	16	76.3	16	76.4	16	65.7	16	52.6	12
Mt. Sinai	9	81.2	9	70.2	9	76.2	9	73.5	9
University of Texas	12	75.5	12	76.7	12	66.6	10	77.3	10
Wayne State University	6	54.1	6	60.7	3	69.8 1/			
St. Christopher's Hospital	8	69.0	8	68.3	8	66.5	8	79.3	8
Harvard University	18	67.4	18	59.1	18	66.2	14	42.1 5/	10
Children's Hospital - Columbus	6	95.9	6	91.5 1/					
Univ. of California, S. F.	18	69.6	18	72.5	18	60.7	18	73.0	18
University Hosp. of Cleveland	10	71.5	10	75.9	8	90.8	6	122.3	8
Stanford University	6	85.1	6	76.3	6	59.1	6	59.6	6
University of Florida	10	56.4	8	72.4	8	64.0	7	77.4	7
Univ. of California, S. F.	9	55.6	9	50.1	9	57.3	9	48.2 5/	9
Children's Hospital, Pittsburgh	6	65.3	6	68.9	5	57.8	6	164.9 4/	6
Children's Hospital, L. A.	6	67.5	6	73.4	6	72.5	6	80.3	6
Mass. Institute of Technology	10	106.5	10	122.7	12	85.4	12	88.7	12
Vanderbilt University	21	61.9	21	66.5	21	91.1	21	82.9	21
N.Y.U., Bellevue	13	97.5	13	73.3	13	85.9	13	91.9	13
Rockefeller University	30	71.5	30	88.9	30	77.1	30	91.2	30
Philadelphia General Hospital	5	86.5	8	55.3	4	71.9	8	50.4 1/	
University of Vermont	6	60.6	6	86.2	6	77.5	6	62.3	6
Children's Hospital, Cinn.	8	62.8	8	57.6	8	60.5	8	60.5	8
Yale University	16	55.0	16	69.2	16	59.0	14	70.5	14
Children's Hosp. Med. Ctr., Boston	10	58.3	10	60.2	10	61.2	10	67.6	10
University of Washington	6	79.3	6	68.2	6	70.6	6	83.0	6
Baylor University	6	90.0	6	84.2	6	83.7	6	107.9	6
Baylor University	8	56.4	8	47.8 5/	6	70.5	6	74.8	6
Children's Mem. Hosp., Chicago	6	88.5	6	72.5	6	76.4	6	76.9 4/	6
Case Western Reserve	8	78.0	8	88.6	8	73.5	8	91.5	8
University of Tennessee	10	71.3	10	68.8	6	69.8	6	79.3	6
St. Univ. of N.Y., Syracuse	10	79.0	10	64.0	10	64.1	10	68.3	6
Children's Hosp. of Phila.	4	75.3	4	85.3	4	80.7	8	60.2	8
University of Miami	14	69.0	14	68.5	14	65.7	14	72.6	10

	FY 1971		FY 1972		FY 1973		FY 1974 3/		FY 1975 6/
	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds Funded
Roswell Park	10	118.4	10	116.8	10	136.0	10	175.3	10
Children's Hospital, D. C.	8	48.3 5/	8	46.8 5/	5	57.9	5	53.4	5
University of Missouri	6	78.3	6	88.5	6	80.7	9	57.8	9
University of Virginia	10	64.2	5	91.6	5	79.6 1/			
University of Chicago	5	82.6	5	58.8	6	65.4	6	50.5	6
St. U. of N. Y., Downstate	10	57.0	10	63.4	8	74.3	8	72.0	8
University of Pennsylvania	5	90.7	5	46.6 5/	5	50.0 5/	3	113.6 1/	4/
University of Oregon	4	66.7	4	71.7	4	91.8	4	72.5	4
Bowman Gray	6	57.3	6	64.1	6	83.7	4	78.3	4
Temple University	5	145.3	5	104.2	8	75.9	8	75.7	8
Baylor University	12	108.8	14	68.8	14	65.6	12	74.8	14
University of Minnesota	11	56.6	11	69.6	11	56.3	8	73.7	10
Harbor General Hospital	8	66.0	8	81.1	8	89.0	8	73.2	9
Boston University	8	60.6	8	63.2	8	57.9	8	51.6	8
Mayo Foundation	13	77.7	13	77.7	12	57.1	12	57.8	12
University of Mississippi					5	96.7	5	67.5	5
Children's Hosp. of Buffalo	6	40.6 5/	6	48.2 5/	6	56.2	5	63.7	6
University of Texas							12	76.8	12
Columbia University					4	61.3	4	79.9	4
University of Arizona					2	85.8	2	95.3	
Albany Medical Center					8	56.2	6	51.5	6
Indiana University					4	60.2	8	61.7	8
Univ. of California, L. A.							8	83.6	8
University of Virginia							7	59.6	7
Scripps Clinic							6		6
University of Kansas							5	141.5 4/	5
Univ. of California, San Diego							8		8
Johns Hopkins University									(Outpatient Center)
Total Beds Funded	885		898		879		880		828
Total Patient Days		240,173 2/		240,490 2/		237,661 2/		245,940 2/	218,500 est.
Total Occupancy		74.4%		73.4%		74.1%		79.6%	75.0% est.

1/ Terminated for scientific considerations.
2/ Total includes patient days paid by third parties and outpatients (3 outpatient visits = 1 patient day)
(Continued)

3/ Occupancies are computed on a slightly different basis in FY 1974 i.e. a "days open" basis. Thus, clearly identified blocks of time in which Centers were closed for vacations, holidays, moving, etc., were excluded from the denominator (bed days available) in the calculation of occupancy. This resulted in an approximate 3% increase in average occupancy. The bed days available by this method was 309,871 days for 880 beds whereas it would have been 880 beds x 365 days, = 321,200 on a 365 day basis. See text.

4/ Mixed Center - a Center that has both research and nonresearch patients occupy beds in the unit. Using nonresearch patients helps offset the cost of personnel at the Center. This provides a flexible method to adjust to the changing needs for research patients and has been utilized to maximize the use of research funds in certain centers. For example in a 10-bed capacity center in which 5 beds are supported for research, the staff used to cover 5 beds maybe capable of covering 10 beds. By allowing the hospital to use the staff for nonresearch patients, this helps offset the costs for center personnel, which would normally be supported entirely by the grant. This "mixed unit" concept requires careful administrative control and is not possible in many centers because "some nonresearch patients are so ill that caring for them on a research center diverts personnel from their research tasks, thereby defeating the purpose of the research unit." (See text) Nonresearch patients were included for this particular analysis to reflect the overall activity of the units on a Program wide basis.

5/ For occupancies of less than 50% see preceding justification.

6/ Data insufficient for FY 1975 to show occupancy comparability on a center-by-center basis. Overall occupancy rate estimated.

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Mr. FLOOD. Last year you told us that the overall occupancy rate was 72.7 percent. That was for the first 6 months now of 1974. What was the final overall occupancy rate for the entire fiscal year 1974?

Dr. BOWERY. According to our information that ran 74.3 percent for inpatients which is comparable to the 72.7 percent figure you just quoted.

Mr. FLOOD. There was testimony last year by Dr. Stone that a good hospital administrator attempts to run on an occupancy rate of 85 percent. That is what he told us. We take a look at this table that you submitted for the record we talked about. We saw a lot of these centers with occupancy rates as low as 43 percent.

If that is so, it appears to us that you must be "renting" too many beds in some of these centers. What about that?

Dr. BOWERY. I think the position that Dr. Stone spoke about is in most of your normal care hospitals. If you can reach 85 percent you are reaching a truly optimal situation. This is different from a research area where sometimes you cannot hospitalize different types of research patients in the same rooms. There are a number of other factors that make it very difficult to reach that optimal level in a research setting.

The indication of a low occupancy rate such as 40 percent probably occurred in a center in which we were in the process of phasing down their operation and therefore we were reporting a low occupancy rate.

Mr. FLOOD. Take a look at the ones that you did have 40 percent in that area and tell us if that was the reason.

Dr. BOWERY. We will examine that.

[The information follows:]

Analysis of General Clinical Research Centers
With Occupancy Below 50% Between 1971 and 1974

	FY 1971		FY 1972		FY 1973		FY 1974 2/		FY 1975 3/
	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds	% of Occ.	No. of Beds Funded
Albert Einstein	12	49.2	12	39.6	12	64.9	12	78.0	8
University of Pittsburgh	14	48.2	14	34.5	10	43.1	10	60.2	10
Children's Hospital of D. C.	8	48.3	8	46.8	5	57.9	5	53.4	5
Children's Hospital of Buffalo	6	40.6	6	48.2	6	56.2	5	63.7	6
Baylor University (Child)	8	56.4	8	47.8	6	70.5	6	74.8	6
University of Pa. Graduate Hosp.	5	90.7	5	46.6 1/	5	50.0 5/	3	113.0	4/ 5/
University of Washington	16	62.5	16	68.2	16	85.9	16	47.9	12
Harvard University	18	67.4	18	59.1	18	66.2	14	42.1	10
Univ. of California, S. F.	9	55.6	9	50.1	9	57.3	9	48.2	9

1/ Erroneously reported on page 961 of the House Hearings for FY 1975. See text.

2/ Occupancies are computed on a slightly different basis in FY 1974 i.e. a "days open" basis. Thus, clearly identified blocks of time in which Centers were closed for vacations, holidays, moving, etc., were excluded from the denominator (bed days available) in the calculation of occupancy. This results in a slight increase in average occupancy.

3/ Data insufficient for FY 1975 to show occupancy comparability on a center-by-center basis.

4/ Mixed Center - a Center that has both research and nonresearch patients occupying beds in the unit. Using nonresearch patients helps offset the cost of personnel at the Center. This provides a flexible method to adjust to the changing needs for research patients and has been utilized to maximize the use of research funds in certain centers. For example in a 10-bed capacity center in which 5 beds are supported for research, the staff used to cover 5 beds may be capable of covering 10 beds. By allowing the hospital to use the staff for nonresearch patients, this helps offset the costs for center personnel, which would normally be supported entirely by the grant. This "mixed unit" concept requires careful administrative control and is not possible in many centers because "some nonresearch patients are so ill that caring for them on a research center diverts personnel from their research tasks, thereby defeating the purpose of the research unit." (See above text) Nonresearch patients were included for this particular analysis to reflect the overall activity of the units on a Program wide basis.

5/ Phase-out budget awarded for scientific considerations.

The table depicts all centers with occupancies of 50% or below in the year 1971 through 1974. The general approach to managing these centers has been to reduce their size while simultaneously encouraging the grantee institutions to develop new high quality clinical research through recruitment and training of additional clinical research scientists. In these nine centers bed capacity was reduced from 96 beds funded in 1971 to 66 beds funded in 1975. One 5-bed center was phased out on the basis of scientific considerations.

The refractory nature of low occupancy rates on certain centers of high scientific merit is a difficult problem. High occupancy can generally be achieved by admitting nonresearch patients to the research center. However, some nonresearch patients are so ill that caring for them on a research center diverts personnel from their research tasks, thereby defeating the purpose of the research unit. The concept of mixing nonresearch patients with research patients has been successful in a limited number of centers provided the type of patients can be controlled, and provided scheduling of such patients does not interfere with the execution of detailed research plans.

It is most desirable from a research perspective to increase occupancy by increasing the number of high quality projects using the center. This approach requires careful planning at the institutional level over a period of years.

Specific comments regarding each of the above centers follow:

Albert Einstein. Several active investigators left this institution in 1971. This was reflected in a drop in occupancy from 90% to 40% in 1972. A program to increase clinical research at this center was initiated with a gradual increase in occupancy to 78%. It should be noted that this center is funded on the basis of actual utilization rather than the more usual rental basis so that the program pays only the costs of those patients on the center.

University of Pittsburgh. In 1971, a program to increase occupancy was initiated at this center. Plans were made to increase the number of projects using the center. Also plans were made to renovate existing facilities, to improve patient facilities, and to provide better conference and diet space. Center bed size was reduced by 4 beds and the number of investigators using the unit increased gradually from 16 to 30 investigators.

University of Pennsylvania Graduate Hospital. The occupancy rate for this center for 1972 was incorrectly reported in the table beginning on page 961 in the hearings last year. The reported occupancy of 47.7% included occupancy for only 8 months in the numerator and 12 months in the denominator. A corrected computation would show occupancy of 72.4% for 1972. In 1973, on the basis of scientific considerations, this center was awarded a phase-out budget of 40% of the requested operating costs. These funds were used to complete ongoing studies in FY 1973 through FY 1974 at a reduced level, which is reflected in the reported occupancy.

Children's Hospital of the District of Columbia. This 8-bed center was reduced to 5 beds in 1973 consistent with experienced occupancy.

Children's Hospital of Buffalo. The occupancy shown is based on a 365-day operation consistent with the reporting practices of other centers between 1971 and 1973. However, in 1971, as an economy measure consistent with the specific scientific studies at this institution, this center began operations on a 5-day basis, closing for weekends. If occupancy is calculated on an actual days-open basis, the occupancy becomes 59.1% for FY 1971, 66.0% for FY 1972 and 85.8% for FY 1973.

Baylor University - Children's Center. Between FY 1972 and FY 1973, center space was redesigned with improved service areas including new outpatient space. The inpatient area was reduced from 8 to 6 beds with consequent improvement in occupancy.

University of Washington. The University program staff and the GCRC Branch staff have been negotiating the level of activity which will be supported. The number of beds, center size, and possibility of operating a mixed unit are key factors. The number of beds has been reduced to 12 beds from the previous level of 16. The University indicated that the funds awarded during 1974 were sufficient to support an occupancy of only 35 to 40% of 16 beds. Final hospital rates are not available at this date.

Harvard University. This center was moved from the Boston City Hospital to the Beth Israel Hospital during the summer of 1974, shortly after the Harvard Medical Service was discontinued at the Boston City Hospital. Although the center was not closed during this period, admissions were sharply curtailed. The operational start-up at the new Beth Israel center was slow, due to the need for investigators to set up new laboratories. The new center has been reduced to 10 beds from the previous 14.

University of California, San Francisco General Hospital. This 9-bed center is in a building apart from the general hospital which decreases the opportunity for admitting nonresearch or sick research patients to this center. Program staff has taken no action to reduce the bed size of this center because of its location and the cost of hospitalization is paid for actual utilization only and not on the more common "rental basis." While nominally a 9-bed center, in reality this center operates at a 7-bed level. However, while changing the number of funded beds to seven would improve occupancy, this change would not affect the cost of the center.

Mr. FLOOD. It would seem that where you do have a center with this consistently low occupancy rate that we are talking about, say over a period of 2 or 3 years now, you could reduce the number of beds that you "rent," take that money, save it up, and invest it in a new center. Is that possible?

Dr. BOWERY. That is essentially what is occurring. We are taking two corrective actions on what we consider are chronically low occupancy rates. Through the technical merit review system we are examining very closely those centers with low occupancy rates and reducing the number of beds not to be used. Plus the staff is also increasing on-site monitoring of the Centers, and I think we can bring about these corrections of critically low occupancy rates much faster than we have in the past.

Mr. FLOOD. Can you take that money that you save and invest it in a new center?

Dr. BOWERY. A center costs anywhere from $400,000 to $600,000 to get started, but your point is well taken. Yes, that money could be garnered together and placed into new settings with higher occupancy potential.

Mr. FLOOD. No reason why not.

What are you doing to encourage other investigators to use the facilities of the Clinic Research Centers where there are, say, only one or two, not any more than that, primary users of the facility now?

Dr. BOWERY. One of the processes that we are using, that I alluded to in the opening statement, is to continue these interface sessions with each of the Institute's Director and their top staff to point out where the Clinical Research Centers are, the nature of the process to gain access, pointing out whether their Institute is or is not using the Centers, and encouraging them to insure that their investigators work through this system.

The basic decision as to which investigators may use these Centers is made at the institutional level. They determine the scientific merit of individual specific protocols. We are trying to increase the awareness of the existence of the Centers, both within the institutions and with our peers at NIH, to insure that there are, hopefully, long lines of investigators waiting to use those Centers, and thereby increase the occupancy rates.

CHEMICAL BIOLOGICAL INFORMATION HANDLING RESEARCH

Mr. FLOOD. Last year you told us about your drug research information system. You call it Prophet. What kind of people are using that system?

Dr. BOWERY. There has been a steady progression of different types of scientists, originally with groups involved in pharmacology. Now we are getting people involved in research activities dealing with immunology and also those involved in cancer research. The user groups, that is, groups of individuals, have steadily risen from 5 in 1974 to 9 in 1975 and we are predicting about 13 user groups in 1976.

The number of investigators within the groups is moving from the 1974 figure of 40 principal investigators to 60 in 1975 and we estimate some 100 in 1976.

Mr. FLOOD. You also told us they are sharing in the cost. How are they sharing in the cost? To what extent do they share in the cost?

Dr. BOWERY. We don't have the precise figures as to the amount of sharing. What is occurring is that as this system is proving to be very useful to the scientists, they are now requesting funds as part of their individual research grant proposals to the categorical institutes, for the cost of on-line computer service from the PROPHET system. We are predicting in 1976 that there will be some 100 scientists from over 9 States involved in this process.

MINORITY BIOMEDICAL SUPPORT

Mr. FLOOD. How many minority biomedical support grants would you be able to award under this budget?

Dr. BOWERY. We anticipate with this budget a slight decrease from the 71 awards in 1975 to 67 awards in 1976.

Mr. FLOOD. This is the comparison with fiscal 1975 then?

Dr. BOWERY. Yes. There is a decrease from 71 to 67.

Mr. FLOOD. How much more money would you need in order to make the same number of awards in 1976 that you had in 1975?

Dr. BOWERY. For that particular program?

Mr. FLOOD. Yes.

Dr. BOWERY. I don't know that precise answer. I would be pleased to put it in the record.

Mr. FLOOD. Yes; we want to see that.

[The information follows:]

In order to fund the same number of Minority biomedical support grants in 1976 as in 1975 an additional $700,000 would be required.

Dr. BOWERY. The minority biomedical support program has been modified to include the following: minority faculty and students of other than the traditional black colleges; the Southwest where we have a large number of Spanish-speaking Americans; some activity involving potential for native American Indians; and some nonminority institutions which have large numbers of minority students. We estimate the increase to be $3 million.

IMPACT OF RETURN TO 1975 BUDGET LEVEL

Mr. FLOOD. Doctor, if we were to restore your budget to the 1975 level how would you distribute the additional money and why would you make that kind of a distribution? There it is. What are you going to do with it?

Dr. BOWERY. Of the total reduction of $47 million, we would propose to restore $43 million back into the general research support program under the revised guidelines. About $2.6 million would be put back in the laboratory animal sciences and primate research program to enable us to start and meet the need for increased primate breeding capacity which we spoke about earlier; and about $1 million or more back into the General Clinical Research Centers program to stabilize the existing 84 Centers. We currently would anticipate that we may have to start phasing down anywhere from 8 to 12 of those Clinical Research Centers under the present budget.

Mr. FLOOD. Mr. Natcher?

Mr. NATCHER. No questions, Mr. Chairman.

Mr. FLOOD. Mr. Obey?

JUSTIFICATION FOR GENERAL RESEARCH SUPPORT PROGRAM

Mr. OBEY. Let me just play the devil's advocate for a moment.

There are an awful lot of programs that need extra money in this budget. You say if you received last year's level you would put $46 million into your general research.

Dr. BOWERY. That is $43 million, which would maintain last year's level of activity.

Mr. OBEY. Let me just play devil's advocate on that for a moment. Why should we put that amount of money into that area? If this committee had $43 million more to use, why shouldn't we put it directly into the budgets of some of the other Institutes, for instance?

Dr. BOWERY. I think that takes us back to the basic principle of why the Congress many years ago recognized that the categorical research project grant is not the only vehicle for providing funds to institutions. The project grant system creates some imbalances and some pressures within an organization and leaves very little flexibility for the institution to try to determine which sets of priorities it wants to deal with. It certainly leaves very little room to make sudden shifts brought about by the normal emergencies that develop in a research program.

Also, I think the general reseearch support program, or its proposed revisions, enable institutions to start to shift or balance the direction they wish to take programs in relation to the Federal purposes and missions. That is, if they wish to recruit a new team or put together people from a number of departments to attack new problems, some of which we have heard this morning in the environmental health area, the ability to do that rapidly by submitting a series of categorical research project applications, with the normal review process of from 6 to 9 months, is defeated if all your funds must flow through the categorical research route.

Admittedly, that route tends to target more closely on the Federal purpose of each of the categorical programs but it leaves very little flexibility for the institution to determine whether it wants to move in a new specific direction, how fast it can move, and allows little flexibility to respond to emergencies that always arise as one deals with the very fluid situation called biomedical research.

So I feel that there needs to be some percentage of funds available to institutions for their self-determined purposes. The authorizing legislation originally called for up to 15 percent of the total NIH research funds to be available for that purpose.

We are currently running around 4 to 5 percent of last year's budget.

Mr. OBEY. What is the average general research support award?

Dr. BOWERY. Approximately $100,000. They range from probably a low of $15,000 for the institutions very minimally engaged in the NIH-supported research up to a maximum of where we have a cutoff level of $255,000 for the institutions most heavily engaged in biomedical research.

PRIMATE CENTERS

Mr. OBEY. You mentioned the shortage of monkeys earlier. Unless somebody on my staff hasn't been telling something I should know, I don't have any information lately on what is happening in the

University of Wisconsin primate laboratory. Do they have any problems right now in terms of obtaining enough monkeys?

Dr. BOWERY. We have been trying to build up the capacity within each of the primate research centers, one being located in Madison, to upgrade their capacity to be self-sufficient for raising their own animals for their research purposes. We are not yet at that stage and with the proposed budget will not be able to meet that goal certainly not by next year.

In addition, because of the current reductions we are being forced to cut back certain programs within each of the centers and there is a concomitant reduction in staff salary support in a number of the centers.

Mr. OBEY. What kind of reduction would that imply for the Madison Center?

Dr. BOWERY. I don't know, but we have recently negotiated the budgets for 1975 for each of the primate centers and I could supply for the record the impact on the Primate Research Center at Madison.

[The information follows:]

Based on the current level of operations the impact of the fiscal year 1976 budget on the Wisconsin Center would be a reduction of approximately $197,000. This will mean the reduction of at least 2 research units and salary funds for 2 professional staff members, and 10–12 technical and support personnel. It should be noted that the other 6 Centers would suffer similar reductions.

The Wisconsin Center is experiencing difficulty in obtaining sufficient primates for their research programs. The majority of the primates used in this Center are rhesus monkeys which are becoming more difficult to obtain. In fact, we have just learned that the Government of India is reducing the export quota worldwide from 30,000 to 20,000 rhesus monkeys per year.

This Center has established an effective breeding program utilizing its present limited facilities. Due to climatic conditions, the outdoor breeding of primates is not feasible, therefore it is quite expensive to establish breeding facilities for this Center which would supply their total needs.

Mr. OBEY. Thank you.

That is all, Mr. Chairman.

Mr. FLOOD. Mr. Conte.

INSTITUTIONAL SUPPORT

Mr. CONTE. Dr. Bowery, there has been a lot of talk about the syndrome of "those who have, get" when talking about Federal funding of biomedical research. There is often criticism that it is the largest, wealthiest, universities that get the Federal money. Are you aware of this problem, and do you see any solution to it? Is there anything that your division, in particular, is doing or could do to develop specifically the resources of some of the less well-endowed institutions?

Dr. BOWERY. Every grantee institution has some policy regarding the emphasis it should place upon biomedical research. These research policies are reflected in institutional decisions regarding staffing, recruitment, job descriptions, space allocation, construction, alteration and renovation, equipment, facilites, et cetera.

It is NIH policy to support the best of proposals for biomedical and behavioral research. Those institutions that host the largest amount of biomedical and behavioral research are the ones with a major commitment to such research. With increasing size of these research programs

at an institution, certain advantages accrue, such as increasing diversity of central shared research resources and opportunities for collaboration and consultation. One mechanism that affords smaller institutions an opportunity to pursue a policy of greater involvement in biomedical and behavioral research, is general research support program. This program's funds are awarded according to a formula that provides approximately 8½ times as much general research support per dollar of research grant support to the smallest grantees as to the largest.

Another mechanism is under consideration. It is a biomedical research development grant program that would provide support for institutions that do not have enough research activity to receive a general research support grant award so that they might develop their research programs in accordance with their own plans after review and approval in national competition.

In addition to the above DRR opportunities to assure that qualified investigators, outside of "those that have, get" institutions, have access to resource capabilities they need, the biotechnology resources program offers another unique opportunity to meet the needs of qualified investigators at institutions not endowed with biotechnology resources through an "interface" resource.

An "interface" resource is designed to make the capabilities of nationally shareable resources available to local or special groups of the biomedical research community.

An example of "interface" resources is found at Rutgers University where that resource's staff collaborate and provide service for glaucoma investigators at Mt. Sinai Medical School of New York, Washington University, and Johns Hopkins through the capabilities of the Division of Research Resources supported computer resource at Stanford University.

Such sharing results in a more equitable distribution and effective use of limited resource support funds and in the inclusion in the national program of promising talented individuals in institutions now isolated from the capabilities of expensive and specialized equipment developed for biomedical research.

IMPACT OF BUDGET DECREASE

Mr. CONTE. Dr. Bowery, it appears that there is quite a decrease from the 1975 budget—from $128.3 million to $81.1 million. Would you care to comment on the amount of that decrease, and why such a decrease is being made?

Dr. BOWERY. The total decrease from the 1975 budget amounts to $47.2 million. The reduction includes $43 million for the general research support program which eliminates this program in 1976. The decrease also includes $2.6 million for the laboratory animal sciences and primate research program and $1 million for the clinical research program. The balance of $0.6 million is distributed among the Division's remaining programs. Budget restraints in recent years have required that programs be reevaluated to determine the levels of support that should be maintained and where reductions could be made without undue harm.

The general research support program was assessed to have a lower priority among the biomedical programs since the major purpose, that

of building up the institutional biomedical research capabilities, has been accomplished and in the view of the Department, regular NIH research project grants are seen as a superior mechanism for the distribution of available biomedical research funds.

INTERFACING WITH OTHER INSTITUTES

Mr. CONTE. Dr. Bowery, as the result of your interfacing session, what areas have been identified where the Division and the Institutes can work more closely together?

Dr. BOWERY. As a result of the interface sessions we have had to date, several of the Institutes are making their grantees and contractors aware of the Division of Research Resources supported biotechnology resources which are shareable, such as the one million volt electron microscopes at the University of Wisconsin and the University of Colorado. Several of the other Institutes are advising clinical investigators that they support the General Clinical Research Centers at their local institutions and urge them to apply to the local advisory group for utilization of the centers for carrying out clinical protocols. An official NIH-wide coordinating committee has been established to promote such information exchange. We are also working closely with several of the Institutes in the identification of ongoing research activities at the minority institutions we are supporting through the minority biomedical support program. Here, also, an official NIH-wide coordinating committee has been established to foster this type of information exchange.

DIVISION OF RESEARCH RESOURCE'S NEW OBJECTIVES

Mr. CONTE. Dr. Bowery, in your statement you referred to the Division's months of self-study in coming up with a revised overall objective. Would you explain how your new objective is different from your old one? Where is the change in emphasis?

Dr. BOWERY. Our new objective stresses the development and maintenance of research resources which aid the NIH as a whole in carrying out its mission. In the past our major emphasis had been to respond to the research resource needs of the institutions throughout the country which were engaged in carrying out NIH supported biomedical research. In some cases, in the past, these resource needs of the institutions were not totally reflecting contemporary research objectives of the NIH. For example, in the early years of supporting the seven Primate Research Centers, these Centers had wide latitude in determining the breadth of scientific investigation they conducted, within the constraints of allowing only highly meritorious science. Within the past few years, we have directed each center to choose a scientific mission which builds on their strengths and is clearly responsive to the major research objectives of the several NIH Institutes, such as, reproductive biology, cardiovascular physiology, environmental health, etc.

TRAINING

Mr. CONTE. Dr. Bowery, I see that you are phasing out the Division's postdoctoral training grants in 1976. Do you believe that the manpower in your fields of endeavor are in adequate supply?

Dr. BOWERY. Considerable confusion has resulted in the training area due to actions, over the past several years, first aimed at a phase out all training grants, followed by court action compelling the release of impounded funds for training, coupled with several new versions of training emphasizing first an individual postdoctoral type program and later some combination of institutional and individual awards. Attraction of new trainees has been a major problem in view of these uncertainties when contrasted with the opportunities available to veterinarians going into practice or other specialities. Hopefully, the continuation of the national research service awards program, coupled with adequate funding, will provide some badly needed long-range stability to the training area.

We do not feel that an adequate number of individuals are being trained in the field of laboratory animal medicine and science. Evidence for a manpower shortage and training requirement is obtained from a survey of laboratory animal resources and personnel conducted by the Institute of Laboratory Animal Resources, National Research Council—National Academy of Sciences, and an informal list of open positions in the field maintained by the staff of the Animal Resources Branch, Division of Research Resources. Over the past several years, the number of open positions has ranged in number from about 25 to 35. This appears to be a chronic situation where the number of open positions far exceeds the number of people available to fill them. It is our professional judgment that 15–20 newly trained individuals are needed annually.

PROBLEMS IN SUPPLY OF PRIMATES

Mr. CONTE. Dr. Bowery, last year you mentioned the problem with the supply of many research primates, and the need to develop the capacity to eliminate our dependence on imported animals—sort of a primate "Project Independence". This year, there is a decrease in the number of grants and the amount of funding for animal resources. Have you been able to solve the primate supply problem over the past year?

Dr. BOWERY. Unfortunately no. In fact, the supply of nonhuman primates for research purposes is becoming an increasing problem. For example, we have just learned that the Government of India is planning to reduce their export quota worldwide from 30,000 to 20,000 rhesus monkeys this year. Serious shortages of several South American species have also developed. A marked increase in demand for nonhuman primates can be expected in several areas of research if current uncertainities or further restrictions occur relative to the use of humans and human fetuses in research.

We are currently taking a number of steps that will assist in solving the shortage of primates for research. The Assistant Secretary, for Department of Health, Education and Welfare, has appointed a Department of Health, Education and Welfare Primate Supply Steering Committee to coordinate all primate supply activities for the Department. This committee is being expanded to include other Federal agencies that require primates in their research programs. This committee is now working with the Pan American Health Organization to establish cooperative primate programs in several key South Amer-

ican countries in order to increase the exportation of essential New World primates. The second major activity concerns the coordination of the primate breeding programs that have recently been initiated. It is anticipated that additional breeding programs will be implemented in the near future. We feel that the establishment of primate breeding programs to supply our own needs for most of the commonly used species should have a high priority. However, it must be remembered that at least 5 years leadtime and a substantial investment of funds will be required to bring these colonies to full production.

CLINICAL RESEARCH

Mr. CONTE. Dr. Bowery, I see that you are phasing out support for several of your General Clinical Research Centers. Which ones? Why?

Dr. BOWERY. General Clinical Research Centers which will be phased out have not yet been determined due to the nature of the review process. In May and June of each year, the General Clinical Research Centers Committee and the National Advisory Research Resources Council rank all new and renewal applications that were project site visited during the past year according to priority ratings. The ranking is done to help determine which applications should be funded. This annual competition for funds also includes approved but unfunded applications from the previous year's ranking. This May and June, the General Clinical Research Centers Committee and the National Advisory Research Resources Council will review grants to insure that only the most meritorious continue to receive program funds. Factors considered will include the scientific quality and productivity of the center, occupancy, impact upon the institution, availability of other resources, and numbers of investigators using the center.

Over the last several years, funds allocated for the General Clinical Research Centers program have remained stable. All known means of fund savings, such as use of outpatients, third party collections, use of mixed research care units, have been exhausted. Due to pressures of cost increases, it is necessary to reduce the number of centers receiving support.

The States which have centers which will be considered for phaseout of support will be furnished for the record.

[The information follows:]

Maryland
North Carolina
New York
Oregon
California
Illinois
Florida
Texas
Pennsylvania
Mississippi
Virginia
Alabama
Wisconsin
Arizona
Connecticut
Missouri
Oklahoma
Tennessee
Ohio
Washington, D.C.
Vermont
Iowa
Indiana
Minnesota
Colorado

Mr. CONTE. Dr. Bowery, what happens to these clinical research centers when you stop supporting them? Are there alternate funding sources available, or do these centers shrivel up and die?

Dr. BOWERY. The future of a given General Clinical Research Center is not predictable when our program support is terminated. In our experience, the outcome depends upon local institutional conditions such as: the need for a General Clinical Research Center, the desire to revise programs to recompete with existing General Clinical Research Centers, and what research resources are available at the institution. Several types of developments have occurred after the Division's support has phased out. For example, where a portion of the scientific interest tended to focus on one area of research, and this element of the research has been funded by other Institutes at the NIH, there has been a continuation of some clinical research at such institutions. In other situations, the institutions have carried on with private funds, reorganized and/or strengthened their scientific clinical efforts, reapplied for program support. Often, however, other pressures force the utilization of space, personnel and beds for different purposes other than biomedical research after the Division's program support has ended.

Mr. CONTE. Could you tell me about some of the work on better therapies for drug addiction which is being done in your clinical research centers? Was anything found that is better than methadone? How are the results of this research disseminated into the health care main stream?

Dr. BOWERY. For years, an effective method of treatment for drug addiction has been sought. Conventionally, treatment usually consists of two overlapping phases—withdrawal of the drug, detoxification, and rehabilitation of the patient. Optimally, the withdrawal phase would be accomplished by replacing the narcotic with a medicine which would relieve all of the symptoms of physical dependence, is safe and acceptable to the patient, is free from major side effects and yet is not subject to abuse. It would relieve physical dependence without creating or perpetuating it. Currently, methadone given orally comes closest to these specifications. The General Clinical Research Center at Rockefeller University introduced and developed methadone maintenance therapy.

Cyclazocine and naloxone are compounds which antagonize the effects of narcotics and are currently being investigated by several Centers to ascertain their effectiveness in the drug therapy program.

Investigators at General Clinical Research Centers are seeking to gain more insight into the mechanisms of physical dependence. This appears to be a dominant factor in the active phase of addiction and may be an important component of the relapse tendency. This insight is necessary to the development of a safer and more effective treatment of addiction.

A completely effective means of therapy has not been found. Ideally, treatment would permit the addict to become a law-abiding, productive, emotionally stable, and drug-independent member of society. With our present knowledge, there is no one treatment that reliably leads to this global goal. Currently, the treatments vary depending upon which goal is given priority, the subgroups for which the treatment is intended, and the factors that are thought to be most significant in perpetuating the problem. General Clinical Research Centers are involved in ongoing investigations to develop effective therapies for the various phases of rehabilitation as well as elucidating

the causative factors and thereby enhancing preventive aspects of these entities.

The onset of various types of treatment programs has necessitated the development of new and systematic methods of data collection and analysis to determine their effectiveness. Several centers are now involved in computer-based data systems which collects, coordinates and analyzes data from the various treatment programs.

Since the General Clinical Research Centers are usually located in a teaching institution, medical students, house staff, and attending physicians are exposed to the investigations conducted there. Once a new modality is deemed effective, it can be immediately incorporated into the medical practice of the hospital's medical personnel. Results of the research done are published in journals and presented at scientific meetings and seminars, and provides the basis for much of the continuing education which physicians receive after graduating.

GENERAL RESEARCH SUPPORT GRANTS

Mr. CONTE. Dr. Bowery, you are again proposing a phaseout of general research support grants. When we held hearings on the rescission on this, we were told that the institutions which are best able to compete for regular NIH project support tend to be the ones supported under this program. I agree with that reasoning, and I think that a better argument for phaseout couldn't be found. But I wonder if anyone has thought about changing the allocation formula, to give these grants to institutions which are less able to compete for regular project support? Has any consideration been given to that possibility? What would it take to revise the formula, should this program be continued for another year?

Dr. BOWERY. General research support is intended for purposes that are not served by regular NIH categorical project grants. Therefore, we do not feel that there is a duplication in program objectives.

As I stated earlier, the revised formula favors the smaller institutions as measured by the ratio of the size of the general research support award to the amount of project support. As a result, there is an 8½-fold advantage to the smallest general research support grantee over the largest. I believe that any further advantage to the smaller institution would need to be justified in terms of institutional development, which would be better served by a competitive development grant program of the type that we have proposed to this committee. Although general research support can be used by grantees for development purposes, such usage is neither typical nor mandatory. I believe that the formula program should not be designated as a developmental grant because the formula mechanism is not appropriate for that purpose and because the other functions of the formula program are unique and important complements to the project grants.

COMPUTER RESOURCE SHARING

Mr. CONTE. Dr. Bowery, to what extent are you supporting the Sumex system at Stanford? How many researchers are hooked up to this system? Can you give me the cost per user?

Dr. BOWERY. At this stage in the development of this system the Sumex-Air resource is essentially wholly funded by the Division of

Research Resources. The various collaborator projects which use Sumex are independently funded with respect to their manpower and operating expenses. They obtain from Sumex, without charge, access to the computing, and, in most cases, communications facilities in exchange for their participation in the scientific and community building goals of Sumex.

The average annual cost of supporting the Sumex system at Stanford is projected to be $650,000 per year over the first 5-year project period. Even though all of the planned capabilities are not yet complete, the resource now has 171 users across the country with 45 users located at Stanford. The present cost per user is $7,375 per year. As the user community grows to the projected level of 250–300 users, the cost per user will drop by 30–50 percent.

The Sumex-Aim system from the start has been founded on the idea that it was necessary to build a new kind of community effort so that workers at distant sites would be able to cooperate efficiently in the solution of very complex problems utilizing a computer. To do this requires a great deal of dedication, effort, and imagination in the service of others, which is not measured by the numbers of dollars spent per active user at a given time, but by the eventual cumulative value of this pattern of research. The cost of computer access per user is believed to be quite reasonable; and every effort is made to temper this in relation to the highest priority needs of the community it serves. However, the design of Sumex was not founded on the idea of producing the maximum number of computer cycles per dollar or per investigator, regardless of the results that these achieve, but rather to demonstrate a cooperative mode of resource-sharing that would generate the most creative research outcomes from the aggregate efforts of its workers.

MILLION VOLT ELECTRON MICROSCOPE

Mr. CONTE. Dr. Bowery, would you tell me what has been done with your million volt electron microscopes during the past year? Can you give me some examples of research that was done on these scopes that could not have been done on less powerful electron microscopes? How much did these two microscopes cost?

Dr. BOWERY. The million volt electron microscopes are operating as national resources. During the past year 55 percent of the beam time was used by scientists residing outside the host institutions. A total of 66 scientists used the microscopes in a wide variety of investigations. The greater penetrating power of the million volt electrons and the higher resolution gained in the microscope allowed these investigators to observe complex biological structures in three-dimension which are not possible to see in less powerful electron microscopes.

The three-dimensional arrangement of DNA, a genetic material, in intact cell chromosomes is being investigated with the million volt electron microscope. Because of the relatively large size and complexity of chromosome organization, the million volt microscope is especially well suited for its structural analysis.

Whole intact cells which are on the average about one micron thick can be observed in the million volt microscope. Less powerful microscopes have to slice a cell into as many as 10 to 20 serial sections in

order to observe the entire cell. Often detailed relationships between cell components are lost in the reconstructed image obtained from serial sections. Also this process is tedious, time consuming, and expensive. Observation of whole cells in the million volt microscope permits the study of structural organization within the cell. Interaction of various substances such as viruses and drugs with various cell components is currently being investigated.

Since the application of high voltage techniques to biomedical research is in the developmental stage, it is difficult to predict specific health-related progress with this methodology. It is certain however, that the new advances in structural knowledge of biological systems gained with the million volt microscope will lead to better understanding of pathological situations, and with it lead to new therapeutic advances.

The 2 million volt microscopes cost the Division of Research Resources $1.323 million. An additional $500,000 from other agencies was given for the construction of the quarters which house the microscopes.

CHEMICAL BIOLOGICAL INFORMATION HANDLING RESEARCH

Mr. CONTE. Dr. Bowery, you said that you expect four user groups to join the "PROPHET" system each year. Why so few? Is this the kind of system that is too sophisticated for anyone to use?

Dr. BOWERY. PROPHET system user groups are selected in national competition on the basis of the scientific quality and health relevance of their research, their need for PROPHET's unique capabilities, and their ability to contribute to the evaluation and refinement of the system. Each user group involves, on the average, 8 to 10 individual investigators and approximately the same number of research projects. Thus, with the addition of four groups per year, the user community is growing at the rate of about 36 regular users per year. This is a rather substantial pace of expansion, especially when one considers the diversity of scientific activity involving drugs and drug-related phenomena that the PROPHET system serves.

The growth rate of the PROPHET user community is determined primarily by the resources available. The present rate is well matched to the hardware capacity and number of contractor personnel that can be supported with the proposed budget. If additional funds were to be made available, there could be a significant increase in the rate of expansion of the user community. For example, a 30-percent increase in the funding level would make possible more than a 100-percent increase in the growth rate.

There is no cause for concern that the PROPHET system is "too sophisticated for anyone to use." In fact, though unique in its scope and power, PROPHET is substantially easier to use than conventional computer systems for biomedical research. Even novice users frequently can carry out complex computing tasks on their own after only a few hours of instruction or self-study. The same tasks often would require weeks or months of work by an expert programer on a conventional computer system.

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PROGRAM PLANS

Mr. CONTE. Dr. Bowery, do you think that this budget is adequate to do the work which you have been assigned?

Dr. BOWERY. With the exception of the general research support program, for which no funds are requested in 1976, the Division will be able to maintain a reasonable level of effort. However, reductions will be necessary in several areas such as the general clinical research program where the phase-out of approximately four or five centers will be initiated in 1976 and the minority biomedical support program where 67 grants rather than the 71 supported in 1975 will be funded. Activities related to the sharing of biotechnology resources and the increased domestic breeding of primates, for example, could effectively utilize additional funds should these be made available.

Mr. CONTE. That is all, Mr. Chairman.

Mr. FLOOD. Thank you, Doctor.

Dr. BOWERY. Thank you, sir.

Justification of the Budget Estimates

Appropriation Estimate

RESEARCH RESOURCES

To carry out, except as otherwise provided, section 301 and title IV, part I of the Public Health Service Act with respect to research resources and general research support grants. [$127,200,000] *$81,058,000: Provided,* That none of these funds shall be used to pay recipients of the general research support grants programs any amount for indirect expenses in connection with such grants.

For "Research resources" for the period July 1, 1976, through September 30, 1976, $20,265,000.

Language provision	Explanation
Provided, That none of these funds shall be used to pay recipients of the general research support grants programs any amount for indirect expenses in connection with such grants.	There is no authorizing legislation for this provision. The language change is in response to the Conference Report on the Labor/DHEW Appropriation Bill for the fiscal year ending June 30, 1965, which states "For general research support grants, as authorized in section 301 (d) of the Act, there shall be available from appropriations available to the National Institutes of Health for operating expenses ---: Provided, That none of these funds shall be used to pay a recipient of such a grant any amount for indirect expenses in connection with such project". The minority biomedical support grants currently authorized by the same authority do not provide for indirect costs.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Research Resources

Amounts Available for Obligation 1/

	1975 Estimate	1976 Estimate
Appropriation:	$127,200,000	$81,058,000
Comparative transfer for the Rhesus Monkey Supply Program from:		
"National Cancer Institute"	172,000	--
"National Health and Lung Institute"	98,000	--
"National Institute of Dental Research"	22,000	--
"National Institute of Arthritis, Metabolism, and Digestive Diseases"	76,000	--
"National Institute of Neurological Diseases and Stroke"	120,000	--
"National Institute of Allergy and Infectious Diseases"	46,000	--
"National Institute of General Medical Sciences"	22,000	--
"National Institute of Child Health and Human Development"	112,000	--
"National Eye Institute"	76,000	--
"National Institute of Environmental Health Sciences"	6,000	--
Comparative transfer from: "National Institutes of Neurological Diseases and Stroke" (Caribbean Primate Research Center)	300,000	--
Total obligations	128,250,000	81,058,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 - $500,000 - 1976 - $500,000.

SUMMARY OF CHANGES

1975 Estimated Obligations	$128,250,000
1976 Estimated Obligations	81,058,000
Net change	-47,192,000

	1975 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increase:				
A. Built-in:				
1. Annualization of pay increase	--		--	$+23,000
2. Within-grade pay increases	--		--	+20,000
3. One extra day of pay in 1976	--		--	+7,000
4. FTS rate increase	--		--	+12,000
5. Bureau of Employment compensation	--		--	+1,000
6. DHEW-NIH General Expense	--		--	+13,000
7. Increase cost of service and supply	--		--	+3,000
8. Increase cost of postage	--		--	+3,000
9. Program Evaluation	--		--	+83,000
Subtotal				+165,000
B. Program:				
1. Fellowships	-	259,000	--	+96,000
2. Research Management and program research	75	2,654,000	-3	+69,000
Subtotal	75		-3	+165,000
Total increases				+330,000
Decreases:				
A. Built-in:				
1. Payment to the National Institutes of Health "Management Fund" for centrally furnished services	--	--	--	-19,000
Subtotal				-19,000
B. Program:				
1. Research grants:				
a. Clinical Research	--	42,326,000	--	-725,000
b. Biotechnology Research	--	11,231,000	--	-723,000
c. Laboratory Animal Sciences and Primate Research	--	17,494,000	--	-2,480,000
d. General Research Support	--	42,957,000	--	-42,957,000
e. Minority Biomedical Support	--	7,264,000	--	-99,000

SUMMARY OF CHANGES - CONTINUED

	1975 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
2. Fellowships	--	$259,000	--	$-21,000
3. Training	--	175,000	--	-175,000
4. Research and Development Contracts	--	3,890,000	--	-323,000
Subtotal				-47,503,000
Total decreases				-47,522,000
Total, net change				-47,192,000

EXPLANATION OF CHANGES

Increases:

A. Built-in: The increases will provide $165,000 in Research Management and Program Services: 1. $23,000 for annualization of 1975 pay raise cost in 1976; 2. $20,000 for within grade pay increases; 3. $7,000 for one extra day of pay in 1976; 4. $12,000 for increases on Federal Telecommunications System (FTS) rates; 5. $1,000 for increases in Bureau of Employee Compensation rates; 6. $13,000 for the increased costs of the DHEW-NIH General Expense Fund; 7. $3,000 for increase cost of services and supply; 8. $3,000 for postage rate increases; 9. $83,000 for program evaluation.

B. Program:

1. Fellowships: The increase of $304,000 will provide support for continuation of previously awarded grants and two new research training fellowships, making a total of eight research training fellowships receiving support in 1976.

2. Research Management and Program Services:
   a. The increase of $69,000 will provide support for continued program evaluation and management, and other administrative services.

Decreases:

A. Built-in: The decrease of $19,000 for decrease in costs of the NIH Management Fund for centrally furnished services.

B. Program:

1. Research grants:

   a. The decrease of $725,000 will contribute to the reduction in the number of general clinical research centers supported. It is estimated that 72 to 76 centers will be supported in 1976 at approximately the 1975 operating levels and phase-out support will be initiated in several additional centers.

   b. The reduction of $723,000 represents the termination of five Biotechnology research grants in 1975.

   c. The amount of $2,480,000 represents a decrease in funding of $617,000 for the seven established primate centers, and $1,863,000 for completion of approximately 20 Laboratory Animal Sciences grants in 1975.

EXPLANATION OF CHANGES - CONTINUED

d. The budget requests reflects a decrease of $42,957,000 for the General Research Support program since no funds are requested for this program in 1976.

e. The reduction of $99,000 represents a termination of one Minority Biomedical Support grant.

2. Fellowships: The decrease of $21,000 reflects the completion of one fellowship.

3. Training: The decrease of $175,000 is a result of phasing out of the Division's portdoctoral training grants in 1976.

4. Research and Development Contracts: The decrease of $323,000 will reduce the number of contracts in 1976 by one.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
238	Clinical Research.....		$42,619,000		$41,601,000		$-1,018,000
242	Biotechnology Research.....		12,153,000		11,430,000		-723,000
246	Laboratory Animal Sciences and Primate Research.....		19,603,000		16,993,000		-2,610,000
251	General Research Support....		42,957,000		--		-42,957,000
252	Minority Biomedical Support.		7,264,000		7,165,000		-99,000
255	Chemical Biological Information Handling.....		1,000,000		1,000,000		--
257	Research Management and Program Services.....	75	2,654,000	72	2,869,000	-3	+215,000
	Total obligations.....	75	128,250,000	72	81,058,000	-3	-47,192,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	75	72	-3
Full-time equivalent of all other positions	8	8	--
Average number of all employees	78	77	-1
Personnel compensation:			
Permanent positions	$1,314,000	$1,333,000	$+19,000
Positions other than permanent	76,000	78,000	+2,000
Other personnel compensation	10,000	10,000	--
Subtotal personnel compensation	1,400,000	1,421,000	+21,000
Personnel benefits	155,000	157,000	+2,000
Travel and Transportation of persons	123,000	123,000	--
Transportation of things	7,000	7,000	--
Rent- communications and utilities	92,000	96,000	+4,000
Printing and reproduction	40,000	46,000	+6,000
Other Services Project contracts	3,890,000	3,567,000	-323,000
Payment to NIH Management Fund	353,000	334,000	-19,000
Other	451,000	649,000	+198,000
Supplies and materials	18,000	20,000	+2,000
Equipment	15,000	16,000	+1,000
Grants, subsidies and contributions	121,706,000	74,622,000	-47,084,000
Total direct obligations	128,250,000	81,058,000	-47,192,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1975 House Report	
Research and demonstrations grants	
1. The Committee recognized that changed circumstances and the passage of time, while not diminishing the need for these grants, has modified their function and that it may therefore be appropriate for NIH to reconsider the formula and guidelines under which they are awarded with a view to revising eligibility, allocation and usage of these funds. The Committee will expect a report on this prior to the hearings on the 1976 appropriations (page 45).	1. Phase-out of this program is again being requested for reasons previously cited to the Committee. The report requested by the Committee will be provided upon completion and after Departmental review.
1975 Senate Report	
1. The Committee concurs in the House action and agrees with the House Committee on Appropriations that changed circumstances and the passage of time while not diminishing the need for these grants may have changed their function somewhat and that a more contemporary approach should be used as to eligibility requirements, allocation and usage of these funds. It is directed that the DRR provide the Committee with a timely report on the new updated plans for this program (page 67).	1. See Item 1 in the House Report (above).

Authorizing Legislation

Legislation	1976 Authorized	1976 Appropriation requested
Public Health Service Act, Title III, Part A. Section 301--Research and Investigation in general	Indefinite	$80,724,000 2/
Title IV, Part I - National Research Service Awards Act	1/	334,000 2/

1/ Authorization expires June 30, 1975; extension legislation is proposed.
2/ Funding estimate only.

Research Resources

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966 1/	$103,919,000	$105,169,000	$110,469,000	$105,669,000
1967	119,521,000	120,234,000	120,234,000	120,234,000
1968	142,841,000	142,841,000	156,141,000	142,841,000
1969	148,200,000	143,419,000	155,523,000	145,509,000
1970 2/	130,398,000	134,358,000	145,358,000	137,358,000
1971 3/	109,678,000	126,901,000	127,501,000	126,901,000
1972	117,269,000	127,160,000	136,648,000	135,648,000
1973*	99,013,000	135,767,000	143,694,000	135,767,000*
1974	88,626,000	133,316,000	133,994,000	126,935,000 4/
1975	82,700,000	124,370,000 5/	130,000,000	127,200,000
1976	81,058,000			

1/ Excludes the "National Institutes of General Medical Sciences" established as a separate appropriation in 1966.
2/ Excludes Office of International Research portions of which were transferred to the National Institutes of Allergy and Infectious Diseases and the John E. Fogarty International Center.
3/ Excludes the Division of Computer Research and Technology incorporated into the "National Institutes of Health Management Fund" in 1971 and appropriation title changed to "Research Resources".
4/ Appropriation after reduction.
5/ Excludes $1,430,000 for contract funds excluded in House allowance due to lack of authorizing legislation.

*Note: This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

Research Resources

Actual

Year	Bureau of the Budget Allowance	House Allowance	Senate Allowance	Appropriation
1966 1/	$58,719,000	$59,969,000	$60,469,000	$60,469,000
1967	67,821,000	68,534,000	68,534,000	68,534,000
1968	81,141,000	81,141,000	84,641,000	81,141,000
1969	87,500,000	82,719,000	86,900,000	84,809,500
1970 2/	69,698,000	73,658,000	79,658,000	76,658,000
1971 3/	63,701,000	66,201,000	66,801,000	66,320,000
1972	68,069,000	71,948,000	75,948,000	74,981,000
1973	75,009,000	75,073,000	83,000,000	75,073,000*
1974	88,632,000	133,322,000	134,000,000	129,426,000 4/
1975	82,700,000	124,370,000 5/	130,000,000	127,200,000
1976	81,058,000			

1/ Excludes the "National Institute of General Medical Sciences" established as a separate appropriation in 1966.
2/ Excludes the "Office of International Operations", transferred to the "National Institute of Allergy and Infectious Diseases" and "John E. Fogarty International Center for Advanced Study in the Health Sciences" in 1970.
3/ Excludes the Division of Computer Research and Technology incorporated into the "National Institutes of Health Management Fund" in 1971 and appropriation title changed to "Research Resources".
4/ Appropriation after reduction.
5/ Excludes contracts not considered by House due to lacking authorization.

*Note This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

Justification

Research Resources

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Personnel compensation and benefits		$1,555,000		$1,578,000		$+23,000
Positions	75		72		-3	
Other expenses		126,695,000		79,480,000		-47,215,000
Total		128,250,000		81,058,000		-47,192,000

General Statement

The Division of Research Resources develops and supports multi-categorical research resources required for sophisticated health-related research performed nationally at academic institutions, hospitals, and research organizations. These research resources help serve the biomedical research community by providing adequate tools and equipment, the necessary environments, and the funds needed for the underlying support of the fundamental research missions of the categorical Institutes of Health.

Six broad-based programs administered by the Division (Clinical Research, Biotechnology Research, Laboratory Animal Sciences and Primate Research, General Research Support, Minority Biomedical Support, and Chemical Biological Information Handling) make awards for selected resources which are distributed among the Nation's academic and research institutions.

DHEW - National Institutes of Health

CROSSWALK - 1975 Column of 1976 President's Budget

INSTITUTE: Division of Research Resources
(Dollars in thousands)

Program	Research Grants			Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials						
	Non-competing	Competing	Other	Grants	Fellowships				
1. Clinical Research			42,326				293		42,619
2. Biotechnology Research			11,231				922		12,153
3. Laboratory Animal Sciences and Primate Centers			17,494	175	259		1,675		19,603
4. General Research Support ...			42,957						42,957
5. Minority Biomedical Support			7,264						7,264
6. Chemical Biological Information Handling							1,000		1,000
7. Research Management and Program Services								2,654	2,654
Total Obligations			121,272	175	259		3,890	2,654	128,250

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DHEW - National Institutes of Health

CROSSWALK - 1976 Column of 1976 President's Budget

INSTITUTE: Division of Research Resources
(Dollars in thousands)

Program	Research Grants			Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Other Direct Operations	Total
	Regular Program		Specials						
	Non-competing	Competing	Other	Grants	Fellowships				
1. Clinical Research			41,601						41,601
2. Biotechnology Research ...			10,508				922		11,430
3. Laboratory Animal Sciences and Primate Centers			15,014		334		1,645		16,993
4. General Research Support..									
5. Minority Biomedical Support			7,165						7,165
6. Chemical Biological Information Handling ...							1,000		1,000
7. Research Management and Program Services.....								2,869	2,869
Total Obligations			74,288		334		3,567	2,869	81,058

RESEARCH RESOURCES

Budget Mechanism

	1975 Number	1975 FTE 1/	1975 Amount	1976 Number	1976 FTE 1/	1976 Amount
Grants						
Special						
General Clinical Research Centers	84		$42,326,000	72-76		$41,601,000
Biotechnology Resources	47		11,231,000	42		10,508,000
Animal Resources	89		17,494,000	69		15,014,000
General Research Support	461		42,957,000	--		--
Minority Biomedical Support	71		7,264,000	67		7,165,000
Subtotal	754		121,272,000	250-254		74,288,000
Fellowships						
Non-competing	2		51,000	6		244,000
Competing	--		--	--		--
New	4		208,000	*2		90,000
Supplemental	--		--	--		--
Subtotal	6		259,000	8		334,000
Training						
Non-competing	3	6	175,000	--		--
Competing	--	--	--	--		--
New	--	--	--	--		--
Subtotal	3	6	175,000	--		--
Research and Development Contracts			3,890,000			3,567,000
Research Management and Program Services			2,654,000			2,869,000
TOTAL			128,250,000			81,058,000

1/ Full time equivalents

Clinical Research

Authorizing Legislation: (Public Health Service Act, Title III, Part A)

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses ..		$42,619,000		$41,601,000		$-1,018,000
Subactivities:						
Clinical Research.		42,326,000		41,601,000		-725,000
Research and Development Contracts.....		293,000		--		-293,000
Total		42,619,000		41,601,000		-1,018,000
Budget Mechanism:						
Research Grants: Special	184	42,326,000	72 to 76	41,601,000	-8 to -12	-725,000
Research and Development Contracts	1	293,000	--	--	-1	-293,000
Total		42,619,000		41,601,000		-1,018,000

Introduction

The Clinical Research program provides the Nation's leading clinical investigators with the specialized resources and facilities necessary to close the gaps in medical knowledge and to translate the latest laboratory discoveries into improved treatment and care for patients.

Patient oriented investigations within the General Clinical Research Centers (GCRCs) cover the spectrum of medical research, such as cancer therapy, transplatation, obesity, population control, human growth and metabolism, heart disease, high blood pressure, and mental retardation. In these GCRCs, the latest conceptual and technical advances from basic science and animal research are developed into refined tools to understand and to treat human diseases. Although much medical research can be conducted on laboratory animals, eventually it must progress to the clinical level where studies are conducted on human subjects. Human subjects also are essential for studying those diseases and biological processes which are not duplicated in other living creatures.

The GCRCs supported by this program are physically discrete research units located in university affiliated hospitals. The program supports a fixed number of beds

which are directed by a physician and are staffed by specially trained nursing, dietary, and laboratory personnel. This program funds approximately 80 percent of all the extramural research hospital beds supported by NIH nationally.

A clinical research center consists of from 4 to 30 beds, the average number being 11. Each center is a special miniature research hospital consisting of bedrooms, bathrooms, treatment rooms, core laboratories, metabolic diet kitchens, patients' lounge, nurses' station, and conference rooms.

Although most of the GCRCs can accommodate both adults and children, approximately 20 percent of the centers focus on pediatric problems. Also a few have been built around premature infants, maternal-child and acute surgical problems.

Originally, the GCRCs were solely inpatient units. Now all of the centers have been allowed the option of modifying their present facilities in order to increase the use of ambulatory patients as research subjects. About 60 percent of the GCRCs have converted their facilities and personnel to include an outpatient clinical research program. Using outpatients in addition to inpatients in clinical research provides additional research opportunities at lower costs.

Program Plans for 1976

In this Program, the annual ranking of General Clinical Research Centers (GCRCs) competing for renewal support is done in June by the National Advisory Research Resources Council which recommends the actual number and size of Centers to be supported. It is estimated that 72 to 76 Centers will be supported in 1976 at approximately the 1975 operating levels and phase-out support will be initiated in several additional Centers.

Program Plans for 1975

It is estimated that 84 centers will receive support in 1975.

To reduce clinical research costs, an increasing number of outpatients are serving as research patients. The use of outpatients allows a broadening of research areas studied and reduces the cost of clinical research compared to the conventional inpatient methods. A chart showing the increase in the use of outpatients follows:

Number of Patient Days

	1970	1971	1972	1973	1974 (Est.)	1975 (est.)
Inpatients	225,488	215,964	221,179	207,084	228,560	214,830
Outpatient Visits	1,176	13,425	24,657	36,309	40,000	45,000

The following examples show the diversity of categorically supported clinical research conducted within the General Clinical Research Centers:

Heart Diseases

Hardening of the arteries (arteriosclerosis) is a progressive process beginning early in life and eventually resulting in heart attacks, strokes, and kidney failure. The major cause of death in the United States is vascular insufficiency resulting from the hardening of the arteries.

The primary cause of arteriosclerosis appears to be elevated blood lipids (cholesterol, triglycerides, etc.) Several GCRCs have developed methods of measuring cholesterol absorption in order to determine the effects of various

therapeutic agents on cholesterol absorption, metabolism and excretion. Information from these studies will show the role of cholesterol as well as determine appropriate dietary and drug therapy.

Heart attack or myocardial infarction is the most serious result of arteriosclerosis. Investigators at GCRCs are evaluating various pharmacological and mechanical interventions in patients with acute heart attacks in an attempt to reduce its high mortality rate. At other GCRCs, surgical interventions, such as the coronary bypass operation which permits a shunting of blood around the area of obstruction, are being devised and assessed. Another surgical procedure results in a lowering of blood lipids and thereby constitutes a potential preventive as well as therapeutic procedure.

Hypertension

Hypertension, or high blood pressure, if untreated or poorly controlled, will lead to progressive vascular damage, cerebral stroke, or coronary occlusion. A number of General Clinical Research Centers have made significant contributions towards identification of correctable forms of hypertension, leading to cure either by specific medication or surgical procedure. One of these correctable forms of hypertension occurs as a result of a diseased kidney, or inadequate circulation to a normal kidney. As a result of work in GCRCs, physicians are now able to measure the kidney-produced hormone renin in venous blood coming separately from the right and left kidneys. This enables them to detect which kidney is abnormal, and so identify which patients can be cured of their high blood pressure by surgical repair of the blood supply to the abnormal kidney or by removal of an irreversibly damaged kidney. Another new technique uses a radioactive method to draw a map of the adrenal glands, thereby helping the surgeon to locate hormone-producing tumors of the adrenal gland, which can also produce hypertension.

Cancer

Cancer is the second leading cause of death in the United States, accounting for 400,000 deaths annually or one out of every six deaths. An estimated 52 million Americans now living will eventually develop cancer and 34 million of these will die from it unless new methods of prevention or treatment are developed. The following studies are currently under way in GCRCs throughout the country:

1) The study of the human body's resistance to disease offers cancer scientists one of the most promising leads to cancer control. Preliminary reports suggest that administration of compounds which augment the cancer patient's immunologic competence may result in a favorable tumor response.
2) Several GCRCs are involved in identifying the etiologic role of viruses in human cancer with the goal of developing a preventive vaccine for leukemia and other types of cancer.
3) In addition, GCRCs are continually evaluating new synthetic anticancer compounds, and within the past decade have contributed to the development of drug treatment protocols which lead to chemotherapeutic cure of two types of cancer, choriocarcinoma and Wilms' tumor.
4) Early investigations on a GCRC in the area of irradiation was responsible for development of an effective treatment for Hodgkin's disease.

Diabetes

Presently, 3,500,000 diabetics in the United States face the prospect of disability from this disease. Over 4 percent of females and 2 percent of males in the country are or eventually will become diabetic. Diabetes is a generalized chronic metabolic disorder usually developing in subjects with a hereditary

inclination. When the disease is fully developed, it is characterized by loss of weight, weakness, lassitude and failure to grow in children. If the disease is not controlled, secondary abnormalities of small blood vessels appear and ultimately cause kidney failure, blindness, hypertension, congestive heart failure and various neurological disorders.

To date, the definitive biochemical lesion which results in diabetes has not been ascertained, although it is known that the fundamental difficulty is an absolute or relative insulin deficiency. Investigators working on GCRCs have been seeking to discover and understand the complex metabolic interrelationships involved in diabetes. The GCRC at Washington University is investigating the effects of various carbohydrate and caloric intakes on insulin release mechanisms.

Although diabetes can be controlled fairly successfully, most diabetics develop vascular (heart and blood circulation) complications after 15 years or more of the disease and ultimately succumb to kidney failure, stroke, or other vascular disease complications. Although it seems sensible to control the disease as accurately as possible without harming the patient, the fact remains that such control does not predictably alter the prognosis of these complications in later years. Scientists believe that there are other unidentified abnormalities in the diabetic which are not corrected by the administration of insulin. Several GCRCs are attempting to identify these abnormalities and thereby develop a therapeutic regimen capable of altering the prognosis of this disease.

Drug Addiction

Drug addiction is a behavioral pattern of compulsive drug use characterized by an overwhelming involvement in the use of a drug, the procuring of its supply, and a high rate of relapse back to the use of the drug after withdrawal. It is estimated that there may be as many as 500,000 narcotic addicts in the United States.

Conventionally, treatment usually consists of two overlapping phases, detoxification (withdrawal) and rehabilitation of the patient. Currently, methadone therapy, developed and introduced at a GCRC, is the most widely used detoxification treatment. Investigators at other GCRCs are involved in ongoing investigations to develop effective therapies for the various phases of rehabilitation, as well as making clear what factors cause drug abuse and increase the preventitive aspects of drug abuse.

Biotechnology Research

Authorizing Legislation: (Public Health Service Act, Title III, Part A)

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$12,153,000		$11,430,000		$-723,000
Subactivities:						
Biotechnology Research ..		11,231,000		10,508,000		-723,000
Research and Development Contracts		922,000		922,000		--
Total		12,153,000		11,430,000		-723,000
Budget Mechanism:						
Research Grants: Special	47	11,231,000	42	10,508,000	-5	-723,000
Research and Development Contracts	8	922,000	8	922,000	--	--
Total		12,153,000		11,430,000		-723,000

Introduction:

The Biotechnology Resources Program provides biomedical scientists access to highly specialized instruments, methodologies, and staff expert in their use and permits maximum exploitation of new, advanced technologies. Development of new knowledge through health research is subject to many restrictions. One involves technological limitation. Critical research questions often are asked that either cannot be answered with existing technological capability, or require such a large, long effort, that their solution is not attempted. The reduction in these constraints is the goal of the Biotechnology Research Program. This Program establishes a rewarding interplay between biology and medicine on the one hand, and the physical sciences, mathematics, and engineering on the other by emphasing the use of digital computation, mass spectroscopy, nuclear magnetic resonance spectroscopy and electron microscopy.

The evolution of the Biotechnology Research Program has produced an array of diverse resources, all designed to meet one or more specific technological needs of biomedical scientists. As new, advanced technological tools become pertinent to health research, the Program tries to make these tools available to the biomedical community. Most of the new technologies are more sophisticated and costly than their predecessors, because the new emerging resources are more complex, and they require a more highly skilled and specialized technical staff to maintain and

operate them, and to develop applications relevant to health problems. Now that almost all of these resources have been specialized to specific research needs, more meaningful contributions can be made to the biomedical community.

Research Resource Sharing:

The demand for these costly specialized resources has increased. Support has been shifted from resources which served scientists exclusively in their host institutions, to resources which serve scientists throughout the Nation. Establishing nationally shared resources is an economical, scientific and rational way to promote and sustain the broad availability of sophisticated research tools required by modern biomedical research. Now scientists from both small and large institutions can use these costly specialized resources and as a result of their increased participation have helped to maximize the potential use of each resource. This has helped us to get more research from each resource and to make our resource dollars produce more.

Computer Sciences and Technology:

Advances in technologies promise to make computer resources more effective in meeting health research needs. Soon refinements in intercomputer communications techniques will allow specialized resources to serve users throughout broad geographic areas. These refinements also will permit flexible access to a variety of computer capabilities from a single terminal, and allow greater reliability through additional "backup" facilities. This will permit the introduction of computers into reliability-critical components of research (such as clinical research). Eventually, the deeper understanding of research structure and clinical information coupled with advances in goal-directed computer programs will increase the usefulness of health information data bases for individual biomedical investigators and the research community.

Program Plans 1976:

Within the total funds available continued support will be provided to 39 resources for the development and shared use of sophisticated equipment in such areas as digital computation, mass spectroscopy, nuclear magnetic resonance spectroscopy and electron microscopy as tools for use in biomedical research. Emphasis will be continued in the application of technology to clinical problems.

Program Plans 1975:

It is estimated that 39 resource grants will be supported in 1975 and continued application of techniques, primarily in computers, to clinical problems will be continued through the contract mechanism.

The following illustrates some of the research activities utilizing biotechnology resources.

Computer Resources

A Nobel prize winner directs the new Stanford University Medical Experimental Computer (SUMEX) supported by the Division of Research Resources. The facility was started in 1974. Its aims are to ensure a nationally shared technological resource for health research promoting the use of artificial intelligence in medicine, and exploring further the application of artificial intelligence in medicine.

Collaborators, who are outstanding experts in their respective fields of glaucoma, infectious diseases, and internal medicine, are organizing their knowledge so it can be stored in the computer. Now many researchers throughout the Nation can interact and work directly with these three experts' knowledge base which is stored in the SUMEX system. Researchers have the expert consultants' knowledge available to them any time and at minimum costs.

Computer-Assisted Decision-Making in Glaucoma Treatment:

Research on the management of medical knowledge relevant to glaucoma diagnosis and therapy at Rutgers University and Mt. Sinai School of Medicine through the use of a computer system is now making clinically significant contributions. A conceptual model of how this knowledge is organized for computer-based problem solving is like that of an iceberg: the visible portion is the set of observed signs and symptoms; at the water line are descriptions of disease states appropriate to the specific patient; and under the water are found the detailed normal and pathophysiological models containing most of what is known about glaucoma-related ocular mechanisms and functions. This computer system is designed to trap inconsistent observations, to be restructured and rebased from new knowledge acquired from the experts in glaucoma as they interact with the system, to provide the rationale for each action recommended, to simulate how each of several glaucoma experts would handle a difficult case, and to provide advice on diagnosis and therapy through the stages of glaucoma. Linkages between experts at different institutions and the Rutgers group are being developed to broaden and deepen this effort and its impact.

Biomedical Applications of Mass Spectrometry

A unique and powerful tool, a combined gas chromatograph/mass spectrometer/gas flow proportional counter system, has been developed at the University of Pittsburgh's Mass Spectrometric Facility for Biomedical Research. This instrument makes it possible to separate the components present in an extract of cells or growth medium, identify them, quantitate each component, and assay their isotope content. From such information an accurate metabolic profile can be determined. For instance, the system is being used to study children with abnormal glucose (blood sugar levels), children with congenital heart diseases, and normal adults. The aim is a better understanding of blood sugar relationships and protein metabolism.

For a number of years there has been considerable interest at the Michigan State University Mass Spectrometric Facility in the structures of fatty substances that are components of normal and abnormal nervous tissue. Studies conducted at this laboratory are designed to elucidate the nature of various neurological diseases through the identification of these materials. Using mass spectral techniques on samples obtained from an 18-month old child, the diagnosis of Sandhoff-Jatzkewitz disease, a rare variant of Tay-Sachs disease, was confirmed.

High Voltage Electron Microscopy (HVEM) Center

Biotechnology Resource activities at the Universities of Wisconsin and Colorado and at the United States Steel Corporation now are providing all qualified scientists throughout the Nation with access to the capabilities of the one million volt electron microscope. This opportunity was almost nonexistent even two years ago.

The million volt beam gives greater penetration of specimens and higher resolution pictures. Small structures inside cells (such as microtubules and ribosomes) are seen with clarity in thick sections without much disruption of their

normal orientation and organization. Virus particles inside cells can be detected much more efficiently than with prior methods (i.e., 10-20 times faster).

These two microscopes were established and are supported with Biotechnology Research Funds. Currently, 30 to 40% of their use has been provided to nonresident investigators drawn throughout the Nation. Making these HVEM resources national facilities is another effort of the Biotechnology Research Program, as part of its resource sharing program. This joint effort will give the Nation's biomedical scientists a broader range of opportunities for using HVEM than any one resource could do alone.

Microelectronics in Medicine

The Biomedical Engineering Resource at Case Western Reserve University is a leader in the practical application of new microelectronic devices and techniques. For example, the resource is developing and evaluating telemetry devices which can be: implanted in the human body to study stress and strain of orthopedic appliances; implanted to monitor intercranial pressure, cerebral spinal fluid pressure, in hydrocephalic (large volumes of fluid within the skull) children; and implanted for chronic monitoring of a patient's condition after organ transplant or other critical surgical procedures.

Implant stimulation devices are being developed which can effect pain suppression by stimulation in the spinal cord or periphery, blood pressure control of hypertensive patients, and control of central nervous system functions.

Using the above devices, systems may be developed to operate an internal signal to control and study the regulation of body functions. More tolerable steps such as providing a bypass for a damaged nervous system network is possible with a system of implanted sensors and stimulators.

Laboratory Animal Sciences and Primate Centers

Authorizing Legislation: (Public Health Service Act, Title III, Part A)

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$19,603,000		$16,993,000		$-2,610,000
Subactivities:						
Laboratory Animal Sciences		7,348,000		5,455,000		-1,893,000
Primate Centers		11,821,000		11,204,000		-617,000
Fellowships		259,000		334,000		+75,000
Training		175,000		--		175,000
Total		19,603,000		16,993,000		-2,610,000
Budget Mechanism:						
Research Grants:						
Special	89	17,494,000	74	15,014,000	--	-2,480,000
Fellowships	11	259,000	15	334,000	+4	+75,000
Training	6	175,000	--	--	-3	-175,000
Research and Development Contracts	10	1,675,000	10	1,645,000	--	-30,000
Total		19,603,000		16,993,000		-2,610,000

Introduction:

The Laboratory Animal Sciences and Primate Research Program assists institutions by providing animal resources for biomedical research and special research environments for scientists to conduct biomedical and behavioral research using nonhuman primates and other animals. The program also provides training grants and fellowship support in laboratory animal science and medicine to assure a continuous supply of research support personnel.

The general objective of this program is to assist institutions by providing the animal resources so vital to biomedical research. The major dependence of health research on the use of animals emphasizes the need for quality animals to be available to a large number of research investigators under conditions which minimizes costs and procurement time. The Laboratory Animal Sciences Program is meeting this need through grant support with the specific objectives of: (a) developing and maintaining laboratories for

the diagnosis and investigation of naturally occurring diseases of laboratory animals; (b) providing new knowledge regarding laboratory animal diseases and optimal husbandry of laboratory animals; (c) defining and elucidating new animal biological models; (d) developing, maintaining, and increasing colonies of special research animals such as primates; (e) gathering and disseminating information regarding laboratory animals; (f) assisting institutions to improve their animal facilities and resources and to meet the requirements of the Animal Welfare Act of 1970 (P.L. 91-579) and HEW policies on the care and treatment of laboratory animals; (g) helping increase the number of primates available for research scientists through programs of domestic breeding of primates.

Research Animal Diagnostic and Investigative Laboratories

A detailed benefit-cost analysis was conducted at the University of Missouri utilizing evaluation funds on two of the 13 Research Animal Diagnostic and Investigative Laboratories supported by the Animal Resources Branch. In total, these 13 laboratories provided disease diagnostic services to 746 NIH supported research projects with an annual funding in excess of $43 million. These diagnostic services are basic to the establishment of disease control programs. In the two laboratories studied, the benefit-cost ratios for diagnostic activities were extremely favorable, being 7.3 to 1 in one laboratory and 10.8 to 1 in the other. In other words, each dollar spent on research animal diagnostic services resulted in a benefit worth $7.30 in one institution and $10.80 in the other. These laboratories also conduct research on relevant disease problems and provide a base for training young investigators on the care and use of research animals. The benefits from these activities are more difficult to measure objectively. Even though extremely conservative assumptions and benefit measures were used, the benefit-cost ratios for research and training always exceeded 1, ranging from 1.1 to 2.9 to 1. Overall the benefit-cost analysis indicated that the laboratories are worth many times their cost.

Animal Facilities and Resources Improvements

A major program area during the past several years has been assisting institutions to improve their animal facilities and resources to meet the requirements of the Animal Welfare Act of 1970 (P.L. 91-579) and HEW policies on the care and treatment of laboratory animals. These awards typically support establishment of central administration and uniform high standards for animal care; training and employment of professional and technical experts in research animal care; and improved physical facilities and equipment. The projects are supported for one to three years, after which time the applicant institution is expected to take over complete financial responsibility for its basic animal resource. In 1974, 34 new awards were made totaling nearly $3 million. There were 1,122 projects ($64 million current annual funding) involving the use of animals which are supported by NIH at the 46 institutions with currently active resource improvement projects.

Research Animal Models

During 1974, the Laboratory Animal Sciences Program supported a total of 22 resources which were related to the development of research animal models and establishment or maintenance of special colonies of valuable experimental animals. The majority of these projects were related to a variety of vertebrate species, including obese strains of rats, Syrian hamsters, degus (South American rodent), inbred and mutant rabbit stocks, frogs, armadillos, Arctic rodent species, etc. Projects of this nature involve particular strains and species for which there is evidence of good

potential usefulness in several research disciplines or disease categories. Efforts of investigators in several disciplines over a rather extensive period are usually required to fully exploit the potential of such models. An example of such activity is:

Development of new lines of Syrian golden hamsters at the Massachusetts Institute of Technology. This colony represents a new genetic pool since the wild hamster stocks under study are the first native animals to enter the United States from Syria since 1930. The Syrian hamster is an important model for many areas of biomedical research and all animals used in the United States are of a very narrow gene pool, being descended from three littermates originally imported in 1930. The investigators are defining and comparing anatomic, physiological, and genetic traits of the newly secured native stocks with the stocks now in common use.

Special Colonies of Research Animals. These projects provide for maintenance of special or unique animal species or strains which serve as institutional and/or national resources. Examples of these activities include:

1. A colony of degus (South American rodent) at the University of Vermont. These animals possess unique anatomic and biological characteristics which make them extremely useful for studies in immunology and development of eye cataracts.

2. A colony of genetically obese rats at the Red Acre Farm, Inc., Stow, Massachusetts. This unique colony serves as a resource for a number of investigators working on nutrient and metabolic aspects of human obesity.

3. Inbred and mutant rabbit stocks resource at the Jackson Laboratory, Bar Harbor, Maine. These specialized stocks represent one of the largest collections of rabbit genotypes in the world and are not duplicated elsewhere. Special genetic models made available from this national resource include those for studies on hemolytic anemia, renal cysts, lymphosarcoma (cancer of the lymph glands) and audiogenic seizures (epilepsy).

National Research Service Awards allow individuals to receive support for research training. These awards provide individuals with postdoctoral research experience in the field of laboratory animal medicine. These awards prepare individuals to provide professional care to many species of laboratory animals, manage central animal resources, and with their superior knowledge of animal biology and understanding of research methods, give special assistance to other investigators. Also, these individuals can train graduate students and new investigators in the use of animals in research, either independantly or as part of a research team. These specialized personnel are in short supply with research positions outnumbering available candidates by four to one.

Primate Research

The closest biological species to man are subhuman primates, and therefore, they are the first choice for many studies of human health and disease; often, they are the only suitable species. Subhuman primates are difficult to breed, expensive to buy, and expensive to maintain. (The price of a juvenile conditioned Rhesus monkey is $150 and costs $1 a day to maintain.) Specimens from the wild carry both apparent and unsuspected monkey diseases and also are susceptible to devastation by human diseases because they lack natural or acquired immunity.

The goals of Primate Research Centers Program include: (a) developing primatology science better to deal with problems of care, disease prevention, diagnosis and treatment, and breeding; (b) providing an environment for research in primates that could not be duplicated elsewhere without difficulty, (c) developing primate models of diseases and conditions; (d) offering training and expertise in primatology to allow multidisciplinary research; (e) reducing primate research costs by helping investigators to avoid costly mistakes in selection and care of primates, and in the design and conduct of experiments with these species.

The Primate Research Centers portion of the Program supports seven Primate Centers which provide unique research environments where multidisciplinary biomedical research in many important areas is being conducted. These Centers are providing national and international leadership in the field of medical primatology, and significant research contributions are made each year in the areas of infectious diseases, cardiovascular diseases, degenerative diseases, reproductive biology, and neural and behavioral disorders. The total 141 core staff scientists conduct research on 134 grants and contracts totaling $7.3 million. A total of 730 scientific publications and books resulted from this research in 1974. In addition, 484 collaborative investigators from a number of universities utilized these facilities to conduct research in 191 NIH supported grants and contracts totaling $14.1 million. An additional 375 scientists were provided with biological specimens. The Centers are active in research and technical training, and a total of 127 graduate students participated in research activities as part of their training. The Centers maintain some 7,800 primates with 3,200 animals in breeding colonies. Currently, the Centers are producing approximately 50 percent of their annual requirement of primates and continue to provide national leadership in primate breeding activities. Examples of recent research findings from the Primate Research Centers include the following:

1. New Diagnostic Method for Renal Cysts:

A new diagnostic technique has been developed at the Delta Primate Research Center that will make surgery unnecessary for more than 100,000 human patients a year who show symptoms of cancer of the kidney. This technique involves the use of various types of endoscopes for visual examination of suspected diseased kidneys in monkeys. This research on nonhuman primates convinced the scientists at this center that the endoscope could be used to examine human patients with suspected cysts of the kidney. There is an association of cysts with malignant tumors in about 2 percent of such cases therefore an accurate diagnosis is necessary and important. By using this device, malignant tumors can be ruled out without resorting to surgery. This new technique has been perfected to the point where it can be used on human patients. It is a simple procedure that avoids the complications of surgery.

2. Hyaline Membrane Disease

The most common cause of death and disability in the human newborn infant is hyaline membrane disease-a consequence of prematurity. Approximately 75,000 infants develop this disease in the U.S. annually, and 25,000 of these will die. To date, no satisfactory model of hyaline membrane disease has been produced in experimental animals which would allow studies of etiology and treatment applicable to the human infant. Hyaline membrane disease is thought to be due to a deficiency of surface active material lining the terminal air spaces within the lung. Unfortunately, there is no satisfactory way to study this deficiency in infants who develop this disease.

Therefore, the experimental production of hyaline membrane disease in the prematurely delivered monkey offers a unique and exceptional opportunity to study mechanisms underlying hyaline membrane disease and methods of accelerating maturation of the fetal lung by pharmacological means. During the past four months investigators at the Washington Center have produced hyaline membrane disease in five prematurely delivered pig-tailed macaque fetuses. It is believed that the development of experimental hyaline membrane disease in the immature monkey provides a very promising area for understanding the cause and treatment of this disease.

3. Leukemia Diagnosis and Treatment

A number of compounds have been isolated from human patients with leukemia that when injected produces antibodies in the blood of chimpanzees. At the Yerkes Center the blood serum containing the antibodies produced by the chimpanzee in response to this treatment have been used to diagnosis the type of leukemia a patient is suffering from and whether the treatment of leukemia patients is successful. This antibody serum also has a potential for the treatment of human leukemia, and clinical trials with human patients will be conducted during the coming year.

Program Plans for Laboratory Animal Sciences and Primate Centers for 1976:

With the total funds available, support will be provided to 67 Laboratory Animal Science projects and 7 Primate Research Centers. Continued support through the contract mechanism will be provided for the domestic breeding of rhesus monkeys. A total of 8 individual and institutional fellowships will be supported. Emphasis will continue to be given to the domestic production of rhesus monkeys in order to supply a portion of the animals required for NIH extramural research programs. The domestic breeding of these animals will offset to some degree the United States dependence on rhesus monkeys imported from India. India, in April 1974, reduced the number of rhesus monkeys it will allow to be exported by 40%.

Program Plans 1975: Support will be provided in the areas of Laboratory Animal Sciences including domestic breeding of rhesus monkeys, postdoctoral training in laboratory animal medicine, and primate research centers. It is estimated that 67 Laboratory Animal Science resources will receive support including 7 new grants, and in addition 7 Primate Centers will be supported. Approximately 9 individual and institutional fellowships will be awarded in 1975.

General Research Support

Authorizing Legislation: (Public Health Service Act, Title III, Part A)

	1975 Base		1976		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$42,957,000		--		$-42,957,000
Total		42,957,000		--		-42,957,000
Budget Mechanism:						
Research Grants						
Special	461	42,957,000		--	-461	-42,957,000

Introduction:

The General Research Support (GRS) Program was initiated in 1962 following the passage of Public Law 86-798. Within the current guidelines, funds awarded to institutions engaged in health-related research supported by NIH and NIMH may be spent for the "Direct Costs" of health research in any appropriate way by recipient institutions. Since 1962, more than $584 million has been allocated to this program.

Program Plans for 1976

Budget restraints in recent years have required a re-evaluation of programs to determine what levels of support should be maintained and where reductions can be made without undue harm. The assessment has been that General Research Support is of relatively lower priority among biomedical research programs and activities. The reasons are as follows:

- A major purpose of the General Research Support Program -- to build up institutional biomedical research capabilities -- has been largely accomplished.

- The larger and relatively more wealthy universities tend to receive the larger dollar awards according to the formula by which the grants are distributed.

- Regular NIH research project grants -- based on competition for funds and peer group scientific review -- are seen as a superior mechanism for the distribution of available biomedical research funds.

Based on this judgment, funds are not proposed for this activity in 1976.

Program Plans for 1975:

In 1975 General Research Support grants will provide support for 461 health professional schools, other academic institutions, hospitals, research institutions, laboratories, centers and certain other nonprofit research organizations heavily engaged in health related research.

Minority Biomedical Support

Authorizing Legislation: (Public Health Service Act, Title III, Part A)

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$7,264,000		$7,165,000		$-99,000
Subactivities:						
Minority Biomedical Support		7,264,000		7,165,000		-99,000
Budget Mechanism:						
Research Grants:						
Special	72	7,264,000	67	7,165,000	-5	-99,000

Introduction:

The Minority Biomedical Support (MBS) Program was initiated in 1972. The MBS Program objectives are to (a) increase ethnic minority participation in biomedical research by adding to the pool of minority scientists, (b) strengthen biomedical research capabilities of minority institutions, and (c) use the talents of minority biomedical investigators. The MBS Program constitutes the major focus and effort of the NIH to involve minority institution scientists and students in biomedical research.

The MBS Program is unique and is not modeled after any other program within NIH. Since it started, the MBS Program has been improved and modified. Institutions now eligible include two-year colleges, and colleges and universities having a large number of ethnic minority students in addition to ethnic minority colleges, universities, and health professional schools.

Significant progress has been made in the types of biomedical research being conducted by ethnic minority faculty and students. For example, at the Second Annual Xavier University MBS Symposium in New Orleans, in April 1974, faculty and students supported through the MBS Program presented 73 papers in biological sciences, 24 in biochemistry and 12 in pharmacology. Faculty and students also have presented papers at Regional AAAS, ACS, Society of Microbiologists and at other meetings.

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Turtle Mountain Counseling and Rehabilitation Center, the first grantee on an American Indian reservation is located in Belcourt, North Dakota, on one of the most densely populated Indian reservations in the United States. Researchers at the Center and Turtle Mountain Community College are investigating problems of alcoholic abuse by the Plains-Ojibay Indians on the reservation. Focusing on the primary social, psychological, cultural, and medical factors associated with alcoholism, these studies also will serve as a national pilot program to suggest new preventive alcoholism techniques to other Indian tribes throughout the United States.

Aided by the Minority Biomedical Support Program (MBS) grant, a major waste water filtering study project is underway at Southeastern State College in Durant, Oklahoma. A series of six lagoons have been constructed and stocked with over one million fish, mussels, and clams by the MBS participants from the predominantly American Indian college. Waste water from Durant's existing sewage treatment facility will run through the lagoons where the fish will eat the nutrients, and the shellfish will lower the concentration of organic material. After 72 hours, the water will be released, allowing communities below Durant to receive potable water, capable of meeting new water standards. With safe, clean water, this method could help eliminate the health and disease risks from untreated or poorly treated waste water.

First-time statistics on lead contamination levels found in mountain streams and lakes in the Rocky Mountain Sangre de Cristo range were compiled by an MBS supported study group at New Mexico Highlands University of Las Vegas, New Mexico. The findings of the predominantly Spanish-speaking American undergraduate researchers in New Mexico have definitely pegged the automobile exhaust emission from traffic-clogged areas as the original source of the lead contamination.

These statistics have been filed with the New Mexico water Resources Research Institute for comparative studies. They will also be used as a barometer for lead contamination levels measured in future testing.

Program Plans 1976:

With the total funds requested for 1976, continued support will be provided to an estimated 67 grants for institutional research programs for involvement of minority scientists in biomedical research and exposure of minority students to the challenges and opportunities in biomedicine.

Program Plans 1975:

An estimated 71 grants supporting 75 minority institutions will be awarded in 1975. Grantees include 55 schools with a predominance of Blacks, 15 schools with a predominance of Spanish speaking people, 3 schools, with a large number of American Indians and 2 schools with a large number of Hawaiian/Polynesian population.

There are 342 faculty investigators receiving support from the MBS Program. The following chart shows the ethnic group of 979 student participants at different levels of education receiving support from the MBS Program:

	Undergraduate	Graduate	Post Doctorates	Total
Black	569	101	11	681
Spanish-speaking	196	19	0	215
American Indian	17	2	0	19
Hawaiian and other Polynesian	26	4	0	30
Oriental	5	3	1	9
Other	24	0	1	25
Total students	837	129	13	979

Chemical Biological Information Handling

Authorizing Legislation: (Public Health Service Act, Title III, Part A)

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$1,000,000		$1,000,000		--
Subactivities:						
Chemical Biological Information Handling..		1,000,000		1,000,000		--
Budget Mechanism:						
Research and Development Contracts	3	1,000,000	3	1,000,000	--	--

Introduction:

The Chemical/Biological Information Handling (CBIH) Program develops and evaluates new computer tools for drug research. The heart of this program is the PROPHET System, a unique computer resource that is shared by a carefully selected community of scientists distributed throughout the country. These scientists are seeking to understand how drugs work. Their ultimate goal is to be able to predict in detail how a new drug or other chemical substance will affect experimental animals and human patients. Such capabilities would do much to reduce the costs of new drug development and to avoid unwanted side effects.

The PROPHET System helps its users by allowing them to deal with larger amounts of data and more complicated types of data than is possible by hand. PROPHET also enables scientists who are widely separated geographically to share data and programs directly with one another through the computer and thereby engage in new forms of collaborative research. PROPHET users are able to conduct experiments that are impossible or impractical without the aid of such a specialized computer. This is the first and only time that a community of geographically dispersed drug investigators has shared a research tool of such scope and power.

There are nine PROPHET user groups at present. They are located in Boston, Mass.; New York, N.Y.; Buffalo, N.Y. (2 user groups); Pittsburgh, Pa.; New Haven, Conn.; Evanston, Ill.; Seattle, Wash.; and Bethesda, Md. Steady growth in the number of users is expected to continue. Moreover, new features are continually being added as a result of the users' experience and suggestions.

Examples of the research objectives of PROPHET users are:

(1) predicting the actions of drugs on the central nervous system through analyses of their shapes and electronic properties;

(2) analyzing the structure of antibodies in order to understand the chemical and genetic mechanism underlying immunity;

(3) studying the three-dimensional shapes of cancer-relevant steroids and relating these structural features to the observed biological activity of these drugs;

(4) studying how the body handles alcohol and other drugs of abuse; and

(5) exploring the uses of computer methods in managing research records of human patients in the clinical pharmacology area.

Program Plans 1976:

The CBIH Program will continue, through the PROPHET System, to demonstrate where and how computer tools can aid drug research. Special emphasis will be placed on evaluating techniques for studying molecular models and for mimicking drug distribution and metabolism within the body. Among the scientific problems to be investigated are the chemical and genetic bases of immunity and the mechanism by which small polypeptide molecules such as angiotensin II affect blood pressure.

Program Plans 1975:

The CBIH Program has (a) enlarged the community of PROPHET users, (b) has made PROPHET more effective and efficient, and (c) has conducted novel experiments in computer-mediated scientific communication in the drug research area. Also, the PROPHET users began sharing in the continuing costs of operating the service. Significant advances were made toward understanding the molecular basis of the action of cancer-relevant steroids and predicting the effects of drugs upon the brain using information about their three-demensional shapes and electronic properties.

Research Management and Program Services

Authorizing Legislation: (Public Health Service Act, Title III, Part A)

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount
Other expenses		$2,654,000		$2,869,000		$+215,000
Subactivities:						
Research Management and Program Services ..	75	2,654,000	72	2,869,000	-3	+215,000

Introduction:

The Research Management and Program Services (RMPS) provides funds for the management, scientific direction and administration of the Division of Research Resources' (DRR) special research programs. The Division is comprised of the following: The Office of the Director, the Program Analysis Branch, and the six special research programs of Clinical Research, Biotechnology Research, Laboratory Animal Sciences and Primate Research, General Research Support, Minority Biomedical Support, and Chemical Biological Information Handling Research.

Research Management and Program Services functions include such activities as program direction, program planning, scientific technical review of grants and contract proposals, administrative services, etc.

Program Plans in 1975 and 1976:

The Division initiated a series of meetings with officials of the categorical Institutes to diffuse information about the types and capabilities of ongoing DRR supported resources on the one hand, and to acquire information regarding the current needs and future plans of the Institutes on the other. This increased interaction will assure that the programs of the Division are responsive to the needs of NIH supported investigators and will aid in the planning of new resource development activities. These meetings will continue in 1976.

During the 1975 Appropriation Hearing in both the House and the Senate, both Houses requested that the Division of Research Resources provide them with a report describing plans for restructuring and strengthening of the General Research Support Programs. A study involving the staff, consultants, and members of the National Advisory Research Resources Council was conducted and a report describing plans for a new formula and guidelines, eligibility requirements, allocation, and usage of these funds was prepared before the 1976 appropriation hearings.

The staff of DRR participates in the NIH Primate Steering Committee which is developing plans for the provision of adequate primate supplies for the NIH's extramural and intramural research work. Additionally, the Division has continued its support to commercial firms and existing primate centers for the domestic breeding of primates for biomedical research. These activities will continue in 1976. The Division will continue to provide the overall direction, coordination, management, and administration of the DRR's programs.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Clinical Research (Public Health Service Act, Title III, Part A)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$42,619,000	Indefinite	--	$41,601,000

Purpose: The Clinical Research program provides the Nation's leading clinical investigators with the specialized resources and facilities necessary to close the gaps in medical knowledge and to translate the latest laboratory discoveries into improved treatment and care for patients.

Explanation: The General Clinical Research Centers (GCRCs) supported through this program are physically discrete research units located in university affiliated hospitals. They consist of from 4 to 30 beds, the average being 11. Each center is a specialized minature research hospital consisting of bedrooms, bathrooms, treatment rooms, core laboratories, metabolic diet kitchens, patients' lounge, nurses' station and conference rooms. Support is provided for a fixed number of beds staffed by specially trained nursing, dietary, and laboratory personnel and directed by a physician.

The applications received by the Program are reviewed by the General Clinical Research Centers Advisory Committee, program staff and the National Advisory Research Resources Council. The staff determines the priorities of awards based on the recommendations of the National Advisory Research Resources Council and the nature of the proposed research described in the application. Approved grants are awarded in yearly increments for a project period of 3 to 5 years. There are no matching fund requirements.

Accomplishments in 1975: During 1975 the program supported 84 clinical research centers in roughly two-thirds of the teaching medical institutions of the nation. Although these centers can accommodate both children and adults, 20% of them focused on pediatric problems. Originally the GCRCs were only inpatient units. Now all the centers have been allowed the option of modifying their present facilities in order to increase the use of ambulatory patients as research subjects. About 60% of the GCRCs have converted their facilities and personnel to include an outpatient clinical research program.

Objectives for 1976: The amount requested for 1976 will support 72 to 76 General Clinical Research Centers at approximately the 1975 operating levels, and phase-out support will be initiated in several additional centers.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Biotechnology Research (Public Health Service Act, Title III, Part A)

1975		1976		
				Budget Estimate
Pos.	Amount	Authorization	Pos.	Amount
--	$12,153,000	Indefinite	--	$11,430,000

Purpose: The Biotechnology Resources Program provides biomedical scientists access to highly specialized instruments and methodologies staffed by experts. This access permits maximum exploitation of new, advanced technologies.

Explanation: The Biotechnology Research program awards grants and contracts for the development and use of sophisticated health-related technologies. Emphasis is placed on digital computation, mass spectroscopy, nuclear magnetic resonance spectroscopy, and electron microscopy. This program's main thrust is to advance biomedical research by creating centers of technological excellence in order to provide the grantees and contractors on NIH's categorical programs with investigative opportunities they otherwise would not have nor could afford. Four component activities characterize the biotechnology resource: (a) the provision for technological and consulting services for biomedical scientists, especially those whose specific projects are funded by the categorical Institutes of the NIH· (b) the conduct of collaborative research with members of the resource user community; (c) the pursuit of research and development directed toward upgrading existing resource capabilities and the state of the technology related to human disease; and (d) the provision of a "base" for the training of biomedical scientists in the use and applications of these technologies.

The Biotechnology Research Program grants are awarded in yearly increments for a project period up to five years and are eligible for renewal. There are no matching fund requirements in this Program. In addition, the contract mechanism is used to support research with non-Federal agencies.

Accomplishments in 1975: It is estimated that 47 resource grants will be supported in 1975 and continued application of techniques, primarily in computers, to clinical problems will be continued through the contract mechanism.

Objectives for 1976: Within the total funds available continued support will be provided to approximately 42 resources for the continued development and shared use of sophisticated equipment in such areas as digital computation, mass spectroscopy, nuclear magnetic resonance spectroscopy and electron microscopy as tools for use in biomedical research. Emphasis will be continued in the application of techniques to clinical problems.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Laboratory Animal Sciences and Primate Research (Public Health Service Act, Title III, Part A)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$19,603,000	Indefinite	--	$16,993,000

Purpose: The Laboratory Animal Sciences and Primate Research Program assists institutions by providing animal resources for biomedical research and special research environments for scientists to conduct biomedical and behavioral research using nonhuman primates and other animals.

Explanation: Project grants for Laboratory Animal Sciences are made to institutions for special animal colonies, research related to improving animal health and care, disease diagnosis and control, studies directed to enhancing the usefulness of animal models for research, improvement of institutional animal facilities and resources to meet requirements of the Animal Welfare Act of 1970, and institutional primate colonies.

The program also provides training grants and fellowship support in laboratory animal science and medicine to asure a continuous supply of research support personnel.

Applications for grant awards are submitted by institutions to the Laboratory Animal Sciences and Primate Research Program. Applications are reviewed by the Animal Resources Advisory Committee, the Primate Research Centers Advisory Committee, program staff, and the National Advisory Research Resources Council. Priorities of awards are determined by staff upon recommendations of the National Advisory Research Resources Council and are based upon the nature of the proposed research described in the application.

The Laboratory Animal Sciences and Primate Research Program grants are awarded in yearly increments for a project period up to five years and are eligible for renewal. There are no matching fund requirements in this Program. In addition the contract mechanism is used to support research with non-Federal agencies.

Accomplishments in 1975: Support will be provided in the areas of Laboratory Animal Sciences including domestic breeding of rhesus monkeys, postdoctoral training in laboratory animal medicine, and primate research centers. It is estimated that 82 Laboratory Animal Science resources will receive support and in addition 7 Primate Centers will be supported. Approximately 9 individual and institutional fellowships will be awarded in 1975.

Objectives for 1976: The FY 1976 budget will provide for the support of 62 Laboratory Animal Science projects and 7 Primate Research Centers. Continued support through the contract mechanism will be provided for the domestic breeding of rhesus monkeys. A total of 8 individual and institutional fellowships will be supported.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: General Research Support (Public Health Service Act, Title III, Part A)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$42,957,000	Indefinite	--	--

Purpose: The General Research Support (GRS) Program was initiated in 1962 following the passage of Public Law 86-798. Within the current guidelines, funds awarded to institutions engaged in health-related research supported by NIH and NIMH may be spent for the "Direct Costs" of health research in any appropriate way by recipient institutions.

Explanation: The GRS Program provides funds on a continuing basis to eligible institutions for their self-determined flexible use in support of biomedical research. Each award is an amount based on the total of the National Institutes of Health and the National Institutes of Mental Health research project grants received by each institution in the preceding fiscal year. Eligible institutions include health professional schools, hospitals, State health departments, research organizations, and non-health professional components of institutions of higher education.

Accomplishments in 1975: The funds available in FY 1975 will provide support for 461 health professional schools, other academic institutions, hospitals, research institutions, laboratories, centers and certain other nonprofit research organizations heavily engaged in health related research.

Objectives for 1976: Because this program is judged to be of lower priority, no funds are provided in the 1976 President's budget for the General Research Support Program.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Minority Biomedical Support (Public Health Service Act, Title III, Part A)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$7,264,000	Indefinite	--	$7,165,000

Purpose: The Minority Biomedical Support (MBS) Program objectives are to (a) increase ethnic minority participation in biomedical research by adding to the pool of minority scientists, (b) strengthen biomedical research capabilities of minority institutions, and (c) use the talents of minority biomedical investigators. The MBS Program constitutes the major focus and effort of the NIH to involve minority institution scientists in biomedical research.

Explanation: The MBS Program was started in 1972 at the encouragement of the Congress. The Program is unique as it is not modeled after any other program within NIH. Since it started, the MBS Program has been improved and modified. Institutions now eligible include two-year colleges, and colleges and universities having a large number of ethnic minority students in addition to ethnic minority colleges, universities and health professional schools.

Applications for grant awards are submitted by institutions to the Minority Biomedical Support Program. Research applications are reviewed by the General Research Support Program Advisory Committee, program staff and the National Advisory Research Resources Council. Priorities of awards are determined by staff upon recommendation of the National Advisory Research Resources Council and are based upon the nature of the proposed research described in the application. The Minority Biomedical Support Program grants normally are awarded for up to five years with funds provided in yearly increments. There are no matching fund requirements.

Accomplishments in 1975: An estimated 71 grants supporting 75 minority institutions will be awarded in 1975. Grantees include 55 schools with a predominance of Blacks, 15 schools with a predominance of Spanish-speaking people, 3 schools with a large number of American Indians and 2 schools with a large number of Hawaiian/Polynesian population. There are 343 faculty and 979 students who will be supported from the MBS Program.

Objectives for 1976: With the total funds requested for 1976, continued support will be provided to an estimated 67 grants for institutional research programs for involvement of minority scientists in biomedical research and exposure of minority students to the challenges and opportunities in biomedicine.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Chemical Biological Information Handling Research (Public Health Service Act, Title III, Part A)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$1,000,000	Indefinite	--	$1,000,000

Purpose: The Chemical Biological Information Handling (CBIH) Program develops and evaluates new computer tools for drug research.

Explanation: The heart of this program is the PROPHET System, a unique computer resource that is shared by a carefully selected community of scientists distributed throughout the country. There are nine user groups at present. These scientists are seeking to understand how drugs work. Their ultimate goal is to be able to predict in detail how a new drug or other chemical substance will affect experimental animals and human patients. Such capabilities would do much to reduce the costs of new drug development and to avoid unwanted side effects.

The PROPHET System helps its users by allowing them to deal with larger amounts of data and more complicated types of data than is possible by hand. PROPHET also enables scientists who are widely separated geographically to share data and programs directly with one another through the computer and thereby engage in new forms of collaborative research. PROPHET users are able to conduct experiments that are impossible or impractical without the aid of such a specialized computer. This is the first and only time that a community of geographically dispersed drug investigators has shared a research tool of such scope and power.

Accomplishments in 1975: The CBIH Program has (a) enlarged the community of PROPHET users, (b) has made PROPHET more effective and efficient, and (c) has conducted novel experiments in computer-mediated scientific communication in the drug research area. Also, the PROPHET users began sharing in the continuing costs of operating the service. Significant advances were made toward understanding the molecular basis of the action of cancer-relevant steroids and predicting the effects of drugs upon the brain using information about their three-dimensional shapes and electronic properties.

Objectives for 1976: The CBIH Program will continue, through the PROPHET System, to demonstrate where and how computer tools can aid drug research. Special emphasis will be placed on evaluating techniques for studying molecular models and for mimicking drug distribution and metabolism within the body. Among the scientific problems to be investigated are the chemical and genetic bases of immunity and the mechanism by which small polypeptide molecules such as angiotensin II affect blood pressure.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Research Management and Program Services (Public Health Service Act, Title III, Part A)

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
75	$2,654,000	Indefinite	72	$2,869,000

Purpose: The Research Management and Program Services (RMPS) provides funds for the management, scientific direction and administration of the Division of Research Resources' (DRR) special research programs.

Explanation: The Division is comprised of the following: the Office of the Director, the Program Analysis Branch, and the six special research programs of Clinical Research, Biotechnology Research, Laboratory Animal Sciences and Primate Research, General Research Support, Minority Biomedical Support, and Chemical Biological Information Handling Research. Research Management and Program Services functions include such activities as program direction, program planning, scientific technical revies of grant and contract proposals, administrative services, etc.

Accomplishments in 1975: The Division initiated a series of meetings with officials of the categorical Institutes for the purpose of diffusing information concerning the types and capabilities of ongoing DRR supported resources, on the one hand, and acquiring information regarding the current needs and future plans of the Institutes on the other. This increased interaction will assure that the programs of the Division are responsive to the needs of investigators supported by the NIH and will aid in the planning of new resource development activities.

A major activity which was undertaken by the Division during 1975 involved a study by staff, consultants, and members of the National Advisory Research Resources Council, regarding the restructuring and strengthening of the General Research Support Programs. This study resulted in a report to the Congress which was requested by both the House and Senate Committees on Appropriations during the review of the 1975 budget.

Another important activity involved the participation of DRR staff in NIH Primate Steering Committee which is developing plans for the provision of adequate primate supplies for the NIH's extramural and intramural research efforts. Additionally, the Division has continued its support to commercial firms and existing primate centers for the domestic breeding of primates for biomedical research.

Objectives for 1976: This activity will continue to provide the overall direction, coordination, management, and administration of the Division's programs. The Division will continue to participate in the development of plans for the provision of adequate primate supplies for the NIH's extramural and intramural research efforts and continue its support to both commercial firms and existing primate centers for the domestic breeding of primates for biomedical research. Meetings with officials of the categorical Institutes will continue for the purpose of diffusing information concerning the types and capabilities of ongoing DRR supported resources, on the one hand, and acquiring information regarding the current needs and future plans of the Institutes on the other.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Research Resources

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$81,058,000	$20,265,000
Total obligations	81,058,000	20,265,000

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Clinical Research	--	$41,601,000	--	$8,550,000
Biotechnology Research	--	11,430,000	--	7,068,000
Laboratory Animal Sciences and Primate Research	--	16,993,000	--	1,237,000
Minority Biomedical Support	--	7,165,000	--	1,705,000
Chemical Biological Information Handling	--	1,000,000	--	900,000
Research Management and Program Services	72	2,869,000	72	805,000
Total obligations	72	81,058,000	72	20,265,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	72	72
Full-time equivalent of all other positions	8	8
Average number of all employees	77	77
Personnel Compensation:		
Permanent Positions	$1,333,000	$333,000
Positions other than permanent	78,000	20,000
Other personnel compensation	10,000	2,000
	1,421,000	355,000
Personnel benefits	157,000	39,000
Travel and transportation of persons	123,000	31,000
Transportation of things	7,000	2,000
Rent, communications and utilities	96,000	24,000
Printing and Reproduction	46,000	12,000
Other Services:		
Project contracts	3,567,000	892,000
Payment to NIH Management Fund	334,000	84,000
Other	649,000	162,000
Supplies and materials	20,000	5,000
Equipment	16,000	4,000
Grants, subsidies and contributions	74,622,000	18,655,000
Total obligations by object	81,058,000	20,265,000

Justification

The estimate for the three-months interim period reflects a continuation of the programs of the Division of Research Resources consistent with the 1976 Estimate. Estimates for individual programs and mechanism were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

52-089 O - 75 -- 77

TUESDAY, APRIL 22, 1975.

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

WITNESSES

DR. MILO D. LEAVITT, JR., DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
GEORGE E. PRESSON, EXECUTIVE OFFICER, JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We have today the John E. Fogarty International Center for Advanced Study in the Health Sciences. It is difficult to say something about John E. Fogarty in a committee like this without remembering John, and he was chairman when I came to the committee for many, many years and did much to breathe life into the operation at NIH for a generation.

We have been trying to follow the great tradition set by Mr. Fogarty when he chaired this committee for so many fruitful years.

All right; the presentation will be made by Dr. Milo D. Leavitt, the Director. I am glad you are the Director. You are not acting anyhow. We have your biographical sketch. It will be placed in the record at this point. You are not new to us, but we do that for all witnesses.

[The information follows:]

Name: Milo David Leavitt, Jr.

Position: Director, John E. Fogarty International Center for Advanced Study in the Health Sciences, NIH.

Birthplace and date: June 24, 1915—Beloit, Wis.

Education: 1933–38—University of Wisconsin, B.A. 1938–40—University of Pennsylvania, M.D. 1945–48—University of Minnesota, M.Sci. 1958–59—Harvard University, M.P.H.

Experience: 1968 to Present—Director, John E. Fogarty International Center for Advanced Study in the Health Sciences, NIH. 1972–73—Member, U.S. Delegation to 25th, 26th and 27th World Health Assemblies, Geneva. 1967–68—Acting Director, Office of Program Planning, NIH. 1967—Deputy Director, Office of Program Planning, NIH. 1966–67—Deputy Assistant Secretary for Science and Population, DHEW. 1966—Science Policy Coordinator, OS–ASH, DHEW, 1962–66—Head, Special International Programs Section, Office of International Research, NIH. 1960–62—Assistant Chief, Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, NIH. 1959–60—Chief, Project Services Branch, Collaborative Research, NINDB, NIH. 1958–59—Postdoctoral Public Health Trainee, Harvard School of Public Health, Boston, Mass. 1949–58—Clinical Assistant Professor Medicine, Medical College of Pennsylvania, Philadelphia, Pa. 1945–49—Fellow, Internal Medicine, Mayo Clinic, Rochester, Minn. 1942–45—Captain, U.S. Army Medical Corps. 1940–42—Rotating Internship, Philadelphia General Hospital, Philadelphia, Pa.

Association membership: American Medical Association. Philadelphia County Medical Society. Society of the Sigma Xi. American Diabetes Association. Association of American Medical Colleges. New York Academy of Sciences. American Association for the Advancement of Science. Industrial Medical Associa-

tion. Alumni Association of the Mayo Foundation. American Public Health Association.

Mr. FLOOD. I see you have a prepared statement, Doctor. How do you want to handle the thing?

Dr. LEAVITT. With your permission, Mr. Chairman, I wish to read it.

Mr. FLOOD. Please do.

OPENING STATEMENT

Dr. LEAVITT. Mr. Chairman and members of the committee, I am pleased to present the programs and the accomplishments of the Center.

Two years ago the Fogarty International Center initiated as a part of its advanced study program a series of comprehensive studies of preventive medicine with a categorical disease orientation for the following purposes:

(1) To review and evaluate the state of the knowledge and research in the prevention and control of human diseases.

(2) To identify knowledge gaps and areas requiring further research including analysis of financial resources, techniques and manpower.

(3) To identify problems in the application of preventive medicine and to suggest corrective actions.

The first planning session of the organizational committee identified 15 major disease categories for detailed review by individual subcommittees. Six subjects were selected for initial consideration: diseases of fetal development and the neonatal period, derangements of dental health, communicable diseases, and the endocrine and metabolic disorders of diebetes and obesity. Workshops have been held on these subjects and manuscripts are now in preparation. It is anticipated that monographs for these subjects will be published or in press prior to June 1975. The two additional subjects: gastrointestinal diseases, and trauma, emergencies and emergency care, are scheduled for the early part of 1976. Additional subcommittees have been activated to consider the subjects of renal disease, nutritional disorders, screening and health status evaluation, diseases of bone and joints, maternal and child health, and economic impact of ill health.

In an effort to coordinate divergent activities in the field of preventive medicine, the Fogarty International Center has also undertaken a cooperative program with the Association of Teachers of Preventive Medicine designed to develop resource material for departments of preventive medicine. This program has the following objectives:

(1) To create resource material for individual departments: To assist in administration, teaching, research, and service among departments of preventive medicine.

(2) To define goals of departments of preventive medicine: To define department mission and enhance collaborative activity among departments of preventive medicine and other departments of health science schools.

(3) To promote cooperative activities among departments of preventive medicine: To propose national programs of joint teaching, research and service, and provide consultative services to other agencies.

Among the 12 topics selected, 7 have been the subject of workshop conferences and are currently in the process of publication.

To further assist in the coordination of thought within the broad area of preventive medicine, the Fogarty International Center has established liaison with the American College of Preventive Medicine and the Association of Schools of Public Health, and is cooperating in the Milbank Memorial Fund Commission for the Study of Higher Education for Public Health.

This multifaceted interest in preventive medicine has provided an opportunity for the Fogarty International Center to assume a coordinating role in the field among various national associations of preventive medicine and public health as well as agencies within the Department of HEW concerned with preventive medicine research and services. It is anticipated that future preventive medicine programs of the Center will emphasize multiagency interests such as studies of factors affecting the implementation of preventive services and evaluation of the efficacy of preventive programs.

GEOGRAPHIC HEALTH STUDIES

The economic situation in the United States during the past 5 years has focused attention upon the U.S. Government's role and its effect upon the economy and various aspects of our society. Among the foremost concerns of leaders of the executive and legislative branches have been that of developing an adequate and equitable health care system in the United States. Similarly, other countries have been facing the problem of attempting to provide adequate health benefits within the framework of a stable economy.

In the United States the degree of congressional attention focused upon these important problems has been exemplified by an increasing number of health related bills introduced into the Congress. Health care delivery systems of other countries have been examined even though foreign health leaders admit that there are elements in their own systems which need improvement. In the United States, some of our leaders are looking toward a much greater governmental involvement in the development and operation of an improved system which would bring adequate health care to all of our population.

During the past 5 years the Fogarty International Center has examined very closely the research, education, and health care in the Soviet Union and the People's Republic of China. Because of the attention focused upon the national health service of the Government of Sweden, the Center has also reviewed that system. The study of the Soviet health system has also enabled us to understand more fully the role of the legislative process, the intricate planning element within a controlled economy, its reliance upon a central and local government relationship, the role of the party, the use of medical assistants, and the role of personalities within this structure.

The massive problems of the People's Republic of China related to a population of over 800 million, limited manpower, and other resources, have focused the Center's attention upon the health problems of that country. Infectious diseases, which were rampant 30 years ago, have been dealt with in an effective manner which has enabled that government to markedly reduce their incidence.

The opening of the People's Republic of China to U.S. physicians has enabled the center to develop a better understanding of our knowledge of medicine and public health in the People's Republic of China.

A number of publications on the U.S.S.R. and the People's Republic of China have been produced which have been used, among other things, as briefing material for physicians and other scientific personnel traveling to those countries. As a result of these and other studies, medical sinologists have initiated a more coordinated effort to studies of traditional medicine and other important aspects of the Chinese health system. Ultimately this improvement in our knowledge should result in a better understanding by American practitioners of the use of traditional medicine in dealing with modern health problems.

FOGARTY SCHOLARS-IN-RESIDENCE

The Fogarty scholars-in-residence program has played an important role in the development of the Fogarty International Center as a Center for advanced study in the health sciences by bringing distinguished scholars from various disciplines to the center to pursue their scholarly interests and to contribute to the academic interests of the National Institutes of Health.

Their interests and contributions have ranged over broad scientific areas; in some cases, their impact and contributions have been direct and readily apparent. For instance:

Professor Torsten Teorell, a distinguished Swedish physiologist from Uppsala University, organized and conducted an international conference on pharmacology and pharmacokinetics during his tenure as a Fogarty Scholar-in-Residence. Professor Teorell was instrumental in bringing to the attention of the scientific community not only the theoretical aspects of drug action and dosage, but their practical application to human patients. These included studies of amphetamine drugs and their relationship to psychiatric disorders, comparative effects of anticlotting agents in the human and laboratory animals, and a consideration of cell and tissue uptake in cancer chemotherapy.

Professor Olavi Eranko, a neuroanatomist from the University of Helsinki, Finland, devoted the major portion of his Fogarty Scholarship to further studies of unique cells (small intensely fluorescent cells) found in nerve tissue and the brain which inhibit the transmission of electrical impulses by releasing a chemical, desoxyphenylamine. It now appears that certain mental diseases, particularly schizophrenia, may be due to disturbances in this mechanism. Professor Eranko's investigations may hopefully lead to more effective methods for treating the patient with mental disease. These findings were discussed at length at a Fogarty Center conference held at the National Institutes of Health February 20–21, 1975.

Dr. Hans Popper, a distinguished American physician and a world authority on diseases of the liver, became a scholar-in-residence last year. Under the aegis of the Fogarty International Center, Dr. Popper fostered the creation and development of a modern nomenclature, diagnostic criteria, and diagnostic methodology for diseases of the liver and biliary tract which will be published later this year.

This international manual of liver diseases provides a worldwide standard on definitions of a confusing variety of liver and biliary-tract disorders of the human being and should enhance the understanding of liver disease throughout the world.

SENIOR INTERNATIONAL FELLOWSHIPS

One of our most interesting program developments has been the initiation of a Senior International Fellowship which is designed to provide opportunities to outstanding faculty members at midcareer from U.S. schools of medicine, osteopathy, dentistry, and public health with demonstrated productive scholarship and recognized stature in their profession to go abroad to study and share their expertise. It is intended that this award be a career enhancing educational experience with mutual benefits to all involved. These research and public health scholarships are intended to:

1. increase the interchange of ideas of mutual interest between U.S. scholars in academic medicine and those of other nations of the world,
2. permit the exchange of the latest advances in a particular area of medicine, both basic and clinical,
3. permit participation in the contribution to ongoing research in the medical sciences or in science areas related to medicine, and
4. improve the academic, research and/or clinical biomedical potential of the U.S. medical institution.

This program, announced in September 1974, has had an enthusiastic response from the U.S. scientific community. Without regard to the very limited time frame within which to qualify for 1975 awards, inquiries have been received from over 400 individuals from 45 States. In addition, at this writing, applications from 25 faculty members representing 21 universities have been received for consideration.

GORGAS MEMORIAL LABORATORY

Mr. Chairman, our request includes $500,000 for the Gorgas Memorial Laboratory. In view of the widespread interest which has been expressed this year in the laboratory, I would like to comment briefly on its activities.

The Gorgas Memorial Laboratory was established in Panama in 1929 as the operating research arm of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc. for which an annual contribution was authorized by the U.S. Congress on May 7, 1928. This contribution was administered by the Department of State until 1955 when the responsibility was transferred to the National Institute of Allergy and Infectious Diseases at NIH. In 1970, the responsibility was transferred to the Fogarty International Center and as you know, the U.S. contribution is $500,000 for the maintenance and operation of the Laboratory.

In 1972, the Institute acquired responsibility for the operation of the Middle America Research Unit (MARU) until then a field laboratory of the National Institute of Allergy and Infectious Diseases located in Ancon, C.Z. During its 15 year history, MARU gained wide international respect for its work on such diseases as hemorrhagic fever, equine encephalitis and hepatitis which was carried out in several countries in Latin America. Although MARU operations are presently financed by annual contracts with NIH, the Gorgas Memorial Institute has affected a consolidation of all its virological work at the MARU center.

Expertise in international health and tropical medicine in the form of basic scientific endeavor as well as systematic advanced education

of selected new candidates is a continuing need of the United States. Leadership in the health professions requires an understanding of disease problems unique in underdeveloped populations, as well as the competence to cope with introductions of exotic diseases into the United States. Finally attempts to ameliorate major human health problems in developing nations is politically rewarding and a laudable objective morally. Thus, the merger of the Gorgas Memorial Laboratory and the Middle America Research Unit assures potential for the development of a unique medical research and educational program in international health.

In conclusion, Mr. Chairman, the budget request for the Fogarty International Center for 1976 is $4,540,000. I shall be pleased to try to answer any questions and supply additional information desired for the record.

GORGAS MEMORIAL INSTITUTE

Mr. FLOOD. Doctor, as you probably know, I am well acquainted with the Panama Canal Zone. As a matter of fact, I am appearing at 2 o'clock before the Merchant Marine and Fisheries Committee of the House having to do with the third lock system and the general question of sovereignty of this country for the Canal Zone.

Your budget calls for $500,000 to help support the work of the Gorgas Memorial Institute, and this level of contribution hasn't changed since 1967; is that right?

Dr. LEAVITT. Yes, sir.

Mr. FLOOD. Do you have any idea what the current operating budget for the Gorgas Memorial Institute is?

Dr. LEAVITT. They have the core support of $500,000 from the Fogarty International Center, a contract from the National Institute of Allergy and Infectious Diseases for the MARU operations in an amount of $696,967 and $589,657 in other grants and contracts. So that brings their present operating budget to $1,786,624.

Mr. FLOOD. All right, but what percentage of the current operating budget is made up from these grants and contracts from the other Institutes out at NIH?

Dr. LEAVITT. We have here a specific breakdown.

Mr. FLOOD. All right. I tell you what you do. I want the percentage, but then will you submit a list of the NIH grants to the Gorgas Memorial Institute in 1975?

Dr. LEAVITT. Yes; we would be pleased to.

[The information follows:]

NIH grants and contracts to the Gorgas Memorial Institute

National Institute of Allergy and Infectious Diseases:	
Ecology of vector-borne viruses	$111,893
Epidemiological studies on leishmaniasis	50,101
Microclimate in ecology of arthropod-borne diseases	24,726
Contract for operation of MARU	696,967
Division of research resources: General research support	12,525
Total	896,212
Percentage of NIH grants to operating budget	50

Mr. FLOOD. Last year, you told us the Department of the Army also supported some of the work at the Gorgas Laboratory. Would you

tell us how much money the Laboratory receives from the Department of Defense and other Federal agencies?

Dr. LEAVITT. Approximately $372,000, sir.

FORMAL RELATIONSHIPS WITH GORGAS MEMORIAL LABORATORY

Mr. FLOOD. We understand the Committee on Foreign Affairs, now International Relations I guess have urged a more formal relationship between the Gorgas Memorial Institute and the Fogarty International Center.

Have you developed a more formal relationship there and if you have how have you done so?

Dr. LEAVITT. Yes, sir, we have. We have participated regularly in executive committee meetings, assisted the Laboratory through the support of onsite scientific program review and with suggestions for their improvement. We have developed plans for an expanded research training center for U.S. and Latin American personnel. We have tried to provide them as much guidance as is appropriate for us.

Mr. FLOOD. Appropriate?

Dr. LEAVITT. Well, appropriate as a Government agency. In the past the role of the Fogarty International Center had not been well defined and we had simply provided a pass-through for the budget. We felt we could be of greater assistance to their programs if we had more direct involvement, as suggested by the Committee on Foreign Affairs. We have felt that there were opportunities for the development of an education resources center and a primate center; that clinical research could be expanded and that more attention should be paid to the practical application of research findings.

RESEARCH ON TROPICAL DISEASES

Mr. FLOOD. In your justification you state that one of the purposes of the Gorgas Memorial Institute is to conduct research on tropical diseases——

Dr. LEAVITT. Yes, sir.

Mr. FLOOD [continuing]. Of public importance to the research of the United States and to Latin America.

Well, can you give us an example of some of the work that the Institute is now doing which is of direct benefit to the citizens of the United States?

Dr. LEAVITT. Yes, sir. For many years the threat of malaria has prompted a worldwide eradication effort. During all this time the Gorgas Memorial Laboratory has continued its studies on malaria control with insecticides and drugs. A major contribution has been the development of monkey models suitable for studies on the treatment of malaria and its immunology. In addition the Laboratory studies on Bolivian hemorrhagic fever, Venezuelan equine encephalitis and yellow fever are of major importance and concern.

Mr. FLOOD. Did you pick some up at the Chucunaque River in Panama where some Indians up the river had yellow fever?

Dr. LEAVITT. Yes.

Returning to malaria, this has not yet been a major problem, but poses a significant threat to the people of the United States. We know now from recent reports that malaria is becoming a major health problem again in India, Sri Lanka (Ceylon), Burma, Thailand and

other areas of Southeast Asia. We know that it is a threat in Vietnam, and it behooves us to be very careful that we are prepared for the introduction of malaria here and know how to cope with it.

The other concern that has been very prominent in the Gorgas operations——

Mr. FLOOD. Will you be giving special attention under the circumstances existing in South Vietnam as of this morning to this problem, vis-a-vis South Vietnam, and the potential influx——

Dr. LEAVITT. The influx of refugees and U.S. citizens?

Mr. FLOOD. Yes.

Dr. LEAVITT. I think in my view this would constitute a threat.

Mr. FLOOD. As of this morning?

Dr. LEAVITT. Yes, sir. We do not have any publicly available documents on malaria in Vietnam, but it is there.

Mr. FLOOD. I imagine you would be curious and alerted to the situation as it now exists and the potential?

Dr. LEAVITT. Yes, sir.

FELLOWSHIPS

Mr. FLOOD. All right; now, how many fellowships are you going to award out there in 1975?

Dr. LEAVITT. Seventy-three.

Mr. FLOOD. Fiscal 1975?

Dr. LEAVITT. 113 during fiscal 1975.

Mr. FLOOD. Can you tell us the total number of individuals that applied for a fellowship? I am talking about the whole thing, all the programs, your scholars in residence, the senior international fellowships, and so on, the whole thing.

Dr. LEAVITT. 250, Mr. Chairman.

Mr. FLOOD. How many fellowships are you going to be able to award in fiscal 1976?

Dr. LEAVITT. Seventy-three.

ANNUAL STIPEND

Mr. FLOOD. This comes up in different ways. What is the annual stipend that you pay up there out of the various fellowship programs you have?

Dr. LEAVITT. The scholars in residence receive a stipend not to exceed $30,000 a year. The international research fellowships are awarded at $14,000 a year, and the senior international fellowships, the new program that is being developed, would not exceed $25,000 in stipend per year.

So the younger man gets $14,000 and the man at midcareer gets no more than $25,000, and the scholar in residence who is much more senior, receives an amount not to exceed $30,000.

Mr. FLOOD. Those scientists are getting $14,000?

Dr. LEAVITT. Yes, sir.

ACUPUNCTURE

Mr. FLOOD. In your opening statement you mention the Fogarty Center has examined very carefully the health care systems, and you mentioned the Soviet Union and China, Sweden. How far have you gone with the acupuncture technique used by the Chinese?

Dr. LEAVITT. We have developed a number of publications on acupncture anesthesia. The latest one came from the press last week. This was developed as a result of our funding a Chinese-American physician who went to the Peoples Republic of China with the development of a report in mind and visited a number of medical centers and wrote the report for us.

HEALTH CARE SYSTEMS

Mr. FLOOD. What did we learn about other health care systems, Chinese, Russian, Swedish; what have you learned about those systems?

Dr. LEAVITT. We have learned that the Chinese and Russian system—well, all three systems you mentioned, Mr. Chairman, provide health care directly to all of the individuals in the country.

Dr. LEAVITT. Well, the thing we have been concerned about——

NATIONAL HEALTH INSURANCE

Mr. FLOOD. Is that national health insurance?

Dr. LEAVITT. No, sir, in those three countries there is a national health service. We are now concerned about the impact of a national health insurance in this country and whether that is going to provide the kind of care that we consider necessary for the people of the United States.

Mr. FLOOD. Can it?

Dr. LEAVITT. Well, I don't know that we are in any position to answer that at this point.

Mr. FLOOD. Until you see what kind of a system it is?

Dr. LEAVITT. Yes, sir; it is in the phase of development or will be in the next few years, and I think it is important for us to learn as much as we can from the experience of other countries.

Mr. FLOOD. You mention Russia, China, Sweden; have you been examining the health care systems of other countries? Do you intend to do that in 1976 besides those three?

Dr. LEAVITT. Yes, sir, we expect to study the Italian experience of national health insurance but not a national health service.

Mr. FLOOD. What is the difference?

Dr. LEAVITT. In a national health service, the Government is the financing agent, as well as the provider of direct service to its citizens. In the case of national health insurance, the Government is the financing agent for services which are, for the most part, provided by the private sector.

Mr. FLOOD. What is the Italian system?

Dr. LEAVITT. That is one that provides medical insurance, health insurance to its people. They have been somewhat disenchanted with it and feel they could provide better care through a national health service. That is why we wanted to examine that system to see what implications it might have for us.

We are also examining the national health insurance in Denmark. That work is underway at the moment.

Mr. FLOOD. That is a national health insurance and a health service system, both?

Dr. LEAVITT. Yes.

COOPERATION WITH OTHER AGENCIES

Mr. FLOOD. All right. Have you involved the staff of the Health Resource Administration, that is charged with the implementation of this new Health Planning and Resource Development Act? Have you involved them in your geographic health studies program?

Dr. LEAVITT. Yes; they are aware of what we are doing.

Mr. FLOOD. You have?

Dr. LEAVITT. Yes, sir. Before the Center embarked on any of these studies, we were in touch with all the agencies within the Public Health Service to avoid any duplication of effort and to keep them informed of what we are doing.

Mr. FLOOD. Then you plan to keep in touch with the HRA staff?

Dr. LEAVITT. Absolutely; it is imperative that we do so.

GORGAS MEMORIAL LABORATORY

Mr. FLOOD. The figures before us, sent up here, contain $500,000 for the maintenance and operation of the Gorgas Memorial Laboratory. Are those funds adequate for the operation of all of these consolidated programs of the Gorgas Memorial Laboratory, for all those consolidated programs for the lab?

Dr. LEAVITT. With the core support provided by us and with the use of contracts and grants, we feel that the previously existing Gorgas program can be maintained at a viable level. However, those funds are not adequate for the consolidated programs.

NEW LEGISLATIVE AUTHORITY

Mr. FLOOD. We are made aware of this—of course you are, too—of the new legislative authority providing for increased financial support for the Gorgas Memorial Institute.

Now, if additional funds were to be made available, how would you utilize those funds, if and when?

Dr. LEAVITT. Should additional funds become available, we would like to aid the development of a regional health research center in Panama. We have assisted in the development of a plan to reorganize the existing facilities and programs of the Gorgas-MARU complex to meet the research and educational needs of the United States and Latin America. We would like to develop an educational resources center, a primate center, and several divisions relating to basic and clinically applied research. In other words, we would like to make the Gorgas Memorial Laboratory an international center for research and training, of interest and usefulness, not only to Panama but to other nations of North and South America.

DIABETES

Mr. FLOOD. All right. Now, Doctor, as you know, the Congress passed the Diabetes Act. That was last year. What sort of work are you doing on diabetes?

Dr. LEAVITT. As I mentioned in our opening statement, we have been concerned with diabetes as part of our preventive medicine program,

and, in fact, expect to develop a whole series of monographs on a variety of diseases and disorders.

Diabetes is one of them. We have at this moment provided information to the National Commission on Diabetes, 27 papers developed under the aegis of the Fogarty Center and its preventive medicine series covering seven major problems that confront the diabetic and produced by 36 contributors from the United States.

Mr. FLOOD. Mr. Patten?

STUDY OF TROPICAL DISEASES AT THE PRESIDIO

Mr. PATTEN. You mentioned exotic diseases. Are you aware of the new facility we built in the last 3 or 4 years to study the tropical diseases at the Presidio in San Francisco under the Army program?

Dr. LEAVITT. I am aware of it, but I do not know the details, Mr. Patten.

Mr. PATTEN. I think we put up $60 million and I presume malaria and skin infections and a lot of other tropical diseases which our people don't see.

I believe in your work; you would have to know what they are doing out there.

Dr. LEAVITT. Yes, sir.

Mr. PATTEN. Should we take the malaria pills on a trip to Egypt?

Dr. LEAVITT. Yes; I personally would take them. I wouldn't want to take any chances. However, we do know that there is a quinine-resistant malaria developing in Southeast Asia. That gives me some pause. Again, this highlights the need for doing more research on malaria and its treatment, because if you have a quinine-resistant case, then problems arise.

Mr. PATTEN. By the way, has the picture changed in 10 years, because it seemed to me that we have 500,000 people over there. I thought some of your fellows came back definitely with malaria from the area. I didn't think there was any question about it.

You say it dried up a little bit and now has come back again in India, and the truth is when we first went to Vietnam, I think malaria was on the front burner, wasn't it? That is my recollection.

Dr. LEAVITT. Yes, sir, then we thought we had it licked or almost licked, and now it is appearing again.

Mr. FLOOD. Of course, malaria will reoccur, too?

Dr. LEAVITT. Yes, sir.

Mr. PATTEN. I have no further questions, Mr. Chairman.

Mr. FLOOD. Mr. Michel?

HEALTH SYSTEMS IN OTHER COUNTRIES

Mr. MICHEL. You say in your statement that during the past 5 years, the Fogarty International Center has examined the health system in the Soviet Union and the People's Republic of China as well as the National Health Service of Sweden. Have we been able to come up with any conclusions regarding the effectiveness of these three countries in meeting their own health needs?

Dr. LEAVITT. On the basis of our studies we believe that the Governments of the USSR, People's Republic of China, and Sweden have produced health care systems which serve the needs of all their people

in an adequate manner consistent with a number of cultural, financial, and geographic factors. Each system is different from the other, the first being a centralized system and the latter decentralized with overall guidance from the national government. Each government is continuously attempting to improve the quality of care for its citizens, examining it from a benefit-cost ratio. Because of the limited access to data on the first two countries, any statement regarding the effectiveness must be qualified. Information on Sweden is much more easily accessible and has resulted in a general admiration by certain American scholars for the quality of care in the Swedish system, despite rising costs and possible need for improvement in the utilization of the system.

Mr. MICHEL. How do you go about relating the things we learn about these other systems to our operations here?

Dr. LEAVITT. The results of studies by the Fogarty International Center of the system in these three countries has resulted in the publication of over 30 documents, which are given wide distribution throughout the public and private sectors of the U.S. health scene. Such documents are distributed to all U.S. medical schools and schools of public health, health administrators, and private physicians in the United States, as well as organizations, societies and medical journals representing the medical community at large. Many publications are used in the curriculum of medical schools and schools of public health in comparative studies of foreign health systems.

Mr. MICHEL. Who does the analyzing?

Dr. LEAVITT. The analysis of these systems is done by scholars of foreign health studies located throughout the United States in both the public and private sectors. Many analysts are located in our medical teaching establishments such as Johns Hopkins University; State University of New York; University of California, Los Angeles; University of Missouri; University of Michigan; University of Chicago; University of Washington; and University of Texas.

HEALTH SYSTEMS IN WESTERN COUNTRIES

Mr. MICHEL. Throughout these hearings, we have heard reference to numerous projects involving the Soviet Union and China. What about some of the other countries, especially the Western European countries? Have you done any research on their health systems?

Dr. LEAVITT. In this phase of our geographic health studies, the center is devoting considerable attention to the experience of Western European countries with different health systems than that in the United States, particularly those countries which have had national health insurance programs for many generations such as Denmark and Italy.

In addition, we are contemplating a detailed study of the Canadian health insurance program, especially the role of central government and provincial government. We have also recently completed a study of some of the changes resulting from the reorganization of the national health system in the United Kingdom, particularly the role of the national health Commissioner and that of the community health officer.

Mr. MICHEL. Wouldn't it be more beneficial for us to have an understanding of the health systems on this side of the Iron Curtain,

since our governments are more closely atuned to each other and, thus, the implementation would be more similar?

Dr. LEAVITT. Yes, sir, we are continuing to examine foreign medical systems in order to determine whether any of their experiences might be helpful to us in the improvement of our own system. This is requiring us to examine the form of political system and the legislative basis for the central and local government roles, of the economic aspects, the social order involved, the historical evolution of the system and other factors. It is our expectation that a more detailed analysis of the systems in the Western European countries will produce information we are seeking for the improvement of an effective health system for all our people consistent with our medical needs and effective use of the resources available. Similarity of situations abroad with those in this country will be a matter of continuing study.

FOGARTY SCHOLARS IN RESIDENCE

Mr. MICHEL. How are our Fogarty scholars in residence selected?

Dr. LEAVITT. Since this is a program by invitation, nominations are made by National Institutes of Health staff, consultants, current and former scholars, and occasionally from the academic sector. These nominations are developed within the center and when appropriate information is obtained, are reviewed by an advisory panel to the scholars in residence program. This panel is made up of seven senior scientists within the National Institutes of Health, three of whom are scientific directors. A group judgment is made as to whether or not the individual under consideration meets the requirements the committee imposes, the most important of which involves the stature of the individual and how he is regarded by his peers, including the contribution the committee feels the individual will make if he or she participates in the program.

Mr. MICHEL. Do you have any figures available on the number of foreign scientists who are interested in becoming a scholar in residence?

Dr. LEAVITT. We have no figures available; however, it would appear based on information received through other scholars that there is considerable interest throughout the world in senior scientists participating in this program. Since many of the nominations come from current as well as former scholars, it is quite likely that those interested and qualified will at some time be involved in the program.

Mr. MICHEL. Where did these scholars come from last year and how long do they stay on an average?

Dr. LEAVITT. During fiscal year 1975, a total of 12 scholars were in residence and they represented the following countries: Israel, Finland, Japan, Germany, Canada, the Netherlands, Sweden, and the United States. The average stay of the scholar is between 6 and 7 months.

SENIOR INTERNATIONAL FELLOWSHIPS

Mr. MICHEL. How many senior international fellowships do you anticipate selecting for this year?

Dr. LEAVITT. Of the total applications we have received to date, we anticipate awarding between 20 and 25.

Mr. MICHEL. Where will our senior fellows go?

Dr. LEAVITT. The applicants' requests for foreign fellowships represent proposed study in 18 countries including the following: West Germany, Italy, Israel, the Netherlands, South Africa, Switzerland, Japan, Lebanon, Scotland, France, Australia, Sweden, Bolivia, Mexico, England, Colombia, The Canal Zone, and Hong Kong.

Mr. MICHEL. Are there specific foreign universities or research centers where you have arrangements already made?

Dr. LEAVITT. No. In this particular program the burden is on the applicant to work out his own arrangements for his fellowship experience.

Mr. MICHEL. Of the 25 applications you have already received, what particular areas are represented in terms of medical expertise?

Dr. LEAVITT. The medical expertise represented is very broad and the categorical disease areas represented include cancer, heart, lung, neurological disorders, basic metabolic disorders, renal physiology, cardiovascular problems, and immunology.

GORGAS MEMORIAL LABORATORY

Mr. MICHEL. How many people are currently involved in research at the Gorgas Memorial Laboratory?

Dr. LEAVITT. There are a total of 158 involved in the research and operations in the consolidated programs of the Gorgas Memorial Laboratory and the Middle America Research Unit which include 15 scientists, 96 technicians, and 47 administrative staff.

Mr. MICHEL. That is all I have, Mr. Chairman.

Mr. FLOOD. Mr. Conte.

SCHOLARS

Mr. CONTE. Dr. Leavitt, you are requesting a decrease of $805,000 in the scholars program. How many scholars did you support last year, and how many do you intend to support this year?

Dr. LEAVITT. We supported 113 scholars in 1975 and are requesting funds to support 73 in 1976.

Mr. CONTE. Are any of these scholar awards multiyear arrangements?

Dr. LEAVITT. None of these awards are funded on a multiyear basis.

Mr. CONTE. Are there any scholars to whom you have moral commitments who will not have their funding renewed in 1976?

Dr. LEAVITT. We are not morally committed to a renewed funding for 1976 although it is expected that our half of the fellows will seek an additional year of support for the completion of their project, which we will be unable to provide.

GORGAS MEMORIAL LABORATORY

Mr. CONTE. This committee has been appropriating $500,000 a year for the Gorgas Memorial Laboratory since 1967. What is the total budget for the Gorgas Laboratory?

Dr. LEAVITT. The total operating budget for the Gorgas Memorial Laboratory in fiscal 1975 is $1,786,624. The total operating budget for 1976 is projected to be $758,750.

Mr. CONTE. What is the total amount it receives from all Federal Government sources, including NIH grants and the Army?

Dr. LEAVITT. Practically all of the operating budget of the Laboratory is derived from Federal Government sources with the core support of $500,000 from the Fogarty Center, $696,967 from the National Institute of Allergy and Infectious Diseases for the operation of the Middle America Research Unit, and $589,657 in grants and contracts. With the exception of $19,000, all this support is from Federal sources.

GEOGRAPHIC HEALTH STUDIES

Mr. CONTE. Your justification refers to the Center's examinations of selected aspects of medicine and health in the Soviet Union and the People's Republic of China. What other countries have you looked at?

Dr. LEAVITT. The Center has examined the national and regional health planning process of Sweden through a study conducted by Dr. Vicente Navarro, Johns Hopkins University. We are also examining certain aspects of medicine and public health in Denmark, the national health insurance program; Canada, the United Kingdom, the role of the health commissioner and the community health officer. In addition, the Center is designing a study of medicine and public health in Latin America which will serve as a reference document for other studies of a more specific nature.

Mr. CONTE. Can you point to some specific aspects of other countries' health care systems that have been integrated into the American system through this program?

Dr. LEAVITT. It would be difficult to pinpoint any specific aspect of systems of other countries which may have been integrated into the American system. Nevertheless, we feel that our studies have produced insights into other systems which cannot help but have an impact on United States considerations. For example, a discussion of the highly centralized systems of the U.S.S.R. and the People's Republic of China highlights the use of professional assistants. This principle is involved in United States thinking about the use of paraprofessional personnel in doctor-shortage areas.

HEALTH PROBLEMS STUDIED AT GORGAS LABORATORY

Mr. CONTE. Would you elaborate upon the health problems which are of mutual interest to the United States and Latin America which are studied at the Gorgas Laboratory?

Dr. LEAVITT. Programs of mutual interest to the United States and Latin America being considered at the Gorgas Laboratory include studies of drug-resistant malaria and ecologic changes associated with major development projects such as river impoundment, highway construction, and land reclamation.

Mr. CONTE. Can you point to some specific recent advances achieved by the Laboratory?

Dr. LEAVITT. Specific advances achieved by the Laboratory include early warning of Venezuelan equine encephalitis which averted a catastrophe in this country 2 years ago, and current efforts to contain yellow fever in Panama and other countries of Central America thus avoiding spread into the Southern part of the United States.

Mr. CONTE. How are these advances institutionalized into tropical health care systems in Latin America and elsewhere?

Dr. LEAVITT. Institutionalization of advances has been partially successful in the area of tropical infectious disease control and treatment. It is anticipated that more emphasis will be placed on institutionalization of recent advances involving prospective study of the relationship between industrialization and chronic diseases of man and evaluation of innovative health care delivery systems in developing countries.

Mr. CONTE. What is the relationship, if any, between the Gorgas Laboratory and the Panamanian Government?

Dr. LEAVITT. Collaboration between the Gorgas Memorial Laboratory and the Panamanian Government has been moderately effective but will receive additional emphasis in the future. Reassessment of program priorities noted previously will facilitate this relationship as well as collaborative activities with other countries of Latin America.

SCHOLARS IN RESIDENCE

Mr. CONTE. Dr. Leavitt, how many scholars-in-residence did you have on record in 1975?

Dr. LEAVITT. We had 12 during 1975.

Mr. CONTE. Who were they, and what did they do?

Dr. LEAVITT. Prof. Michael Sela, chairman, Department of Chemistry, Weizmann Institute, Israel. Dr. Sela is a distinguished immunologist who is involved in studies of protein structure and proper antigen design that may lead to a better understanding of the immune response on a molecular and cellular level.

Prof. Olavi Eranko, chairman, Department of Anatomy, University of Helsinki, Finland, a recognized authority in the field of neurobiology, who devoted the major portion of his Fogarty Scholarship to further studies of unique cells (small intensely fluorescent cells) found in nerve tissue and the brain which inhibit the transmission of electrical impulses by releasing a chemical, desoxyphenylamine.

Prof. Elvin Kabat, Department of Microbiology, Columbia University School of Medicine, a distinguished immunochemist, who, in addition to revising a book in immunochemistry, has been involved in research on protein structure.

Dr. Karl Beyer, former vice president for research of Merck, Sharp and Dohme, a noted pharmacologist with a particular interest in problems of renal physiology. He conducted a number of seminars with intramural scientists of the National Heart and Lung Institute. In addition, he served as an active consultant to the NIH Committee on Dissemination of Research Results which concerned itself with the problem of communication of laboratory results.

Dr. Paul Zamecnik, professor of medicine, Harvard Medical School and director of the Colis P. Huntington Laboratories of the Massachusetts General Hospital is actively pursuing basic work in the field of DNA synthesis with respect to problems of viral origin. Dr. Zamecnik's broad interests are in the field of cancer and he is particularly expert in the field of Hodgkin's disease.

Prof. Dirk van Bekkum, director of the Radiobiology Institute, The Netherlands, is a well known expert in the field of radiobiology. Dr. van Bekkum's interests focus on the broad cancer field and, in particular, bone marrow transplant studies. While a scholar-in-resi-

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dence, he is engaged in research with his scientific colleagues of the National Cancer Institute on bone marrow transplants. It is anticipated that he will develop and conduct an international conference on that subject in mid-June.

Prof. Ragnar Granit, Nobel Laureate and past president of the Nobel Institute of Physiology. Professor Granit's expertise in the field of neuromuscular physiology is of direct relevance to current research going on in the National Institute of Mental Health.

Prof. Ronald Christie, former dean of McGill University, Montreal, Canada is a recognized authority in medical education. During his previous tenure as a Fogarty Scholar he produced a comparative study of medical curriculum and a comparative study of State and private schools within the United States. He is now in residence refining his manuscripts, which the Center expects to publish early in fiscal 1976.

Dr. Abraham Horwitz, until recently Director of PAHO, is the author of articles on infectious diseases, epidemiology, and public health administration. While a scholar-in-residence, he will be undertaking a broad study of malnutrition in Latin America and it is expected that his activity will result in a series of recommendations which, if implemented, will contribute to the solution of nutritional problems in both United States and Latin America.

Prof. Charles Leblond, chairman, Department of Anatomy, McGill University, Montreal, Canada, recently arrived at the Center, will be engaged in studies in the field of histology, in which he is introducing a new concept, namely that of a dynamic rather than the traditional static approach.

Prof. Hideo Nishimura, chairman, Department of Anatomy, Kyoto University Faculty of Medicine, Kyoto, Japan. Professor Nishimura has completed a number of scientific manuscripts concerning research in the field of human embryology and birth defects. He also continued his collaborative work with colleagues at the New York University.

Prof. Theodor Wieland, chairman, Department of Chemistry, Max-Planck Institute, Heidelberg, Germany. An outstanding biochemist, who is known for his many contributions in the field of chemistry, Professor Wieland is interested in biological toxins from a chemical viewpoint.

Mr. CONTE. How many do you expect to have in 1976?

Dr. LEAVITT. We do not anticipate any marked change in the number of scholars and look forward to between 12 and 14 individuals.

INTERNATIONAL RESEARCH FELLOWSHIPS

Mr. CONTE. Yesterday I received phone calls from several doctors in the Boston area who were concerned because their medical schools' International Fellowships were being cut back under the 1976 budget.

Dr. LEAVITT. Although I cannot specifically relate the decrease in the International Research Fellowship program to any particular area or school, it is true that we will fund fewer fellows in 1976 than in 1975.

Mr. CONTE. How many of these International Fellows do you intend to support in 1976?

Dr. LEAVITT. Funds available will permit the award of approximately 30 fellowships.

Mr. CONTE. How does this compare to 1975?

Dr. LEAVITT. This will represent a reduction of 28 fellowships.

Mr. CONTE. Can you give me some examples of the kinds of work done by these fellows?

Dr. LEAVITT. I have with me several citations from both NIH and university scientists about some of our international research fellows and I would like to summarize their accomplishments:

Working in the laboratory of chemistry of the National Institute of Arthritis and Metabolic Diseases, a young scientist from the University of Sydney engaged in work directed at providing a definitive metabolism profile for the environmental carcinogen benzpyrene. His preceptor has stated that this participant had been instrumental in setting up an assay system which will be used in that laboratory for years to come.

From Yale University we have a letter advising that as a result of the work of an international research fellow this program had contributed significantly to the rapid resolution of an important research question of "gene amplification" in the oocytes of Amphibia. It was further stated that the program had contributed to the rapid resolution of an important research question.

From the cardiology branch of the National Heart and Lung Institute is a report of an international fellow from New Zealand who has completed a study designed to determine the mechanisms responsible for the beneficial action nitroglycerin exerts in the treatment of acute myocardial infarction. He accomplished this by devising an extremely well thought out protocol and conducting numerous experiments, the results of which, in the opinion of senior scientists, will ultimately have great impact on the actual treatment of patients with acute myocardial infarction. In addition he has made great strides in perfecting the methodology necessary to measure segmental myocardial functions during acute infarction.

A preceptor of the University of North Carolina reports that his international fellow from Norway has characterized and described the functions of a specific testicular androgen binding protein which is produced in the Sertoli cell and believed to transport antigens from the interstitial compartment into the tubule. His work, in the judgment of the senior scientists at the university, represents a major breakthrough in understanding of the hormonal regulation of spermatogenesis.

We have many other examples of the contributions of these young fellows and will be pleased to provide any additional information. In general, I would say that these fellows are appointed after competitive selection process and are in the outstanding category in terms of biomedical scientific potential.

CONFERENCES AND SEMINARS

Mr. CONTE. How many conferences and seminars do you intend to have in 1976?

Dr. LEAVITT. We anticipate that categorical reviews of the state of the art of preventive medicine will be continued dealing with the subjects of kidney and urinary tract disease, maternal and child health, nutrition, arthritis, injury and screening in health maintenance. In addition major emphasis will be placed on certain aspects of health

education, environmental health, and preventive services in health care delivery. Collaborative activities with other Institutes and Agencies will result in the convening of a total of approximately 25 conferences.

Mr. CONTE. How many will you have in 1975? What were they on?

Dr. LEAVITT. We held 17 conferences in 1975. In addition we commissioned several monographs. I have here a list of those conferences, if I may insert them into the record.

[The information follows:]

CONFERENCES HELD BY THE FOGARTY INTERNATIONAL CENTER DURING 1975

PREVENTIVE MEDICINE AND HEALTH CARE DELIVERY

Prevention of Human Health Problems

Kidney and Urinary Tract Disease.
Anglo-American Conference on Medical Priorities.
Advisory Committee for National Conference on Preventive Medicine.
Health Education Promotion and Behavior Modification.
Education and Training.
Theory, Practice and Application of Prevention in Environmental Health.
Economic Impact.
Inter-American Conference on Maternal and Child Health Services Delivery Systems.
National Conference on Preventive Medicine.
International Health Costs and Expenditures.

Educational Aspects of Preventive Medicine

Preventive Medicine Curriculum Development Project.
Academic Mission of Departments of Family Medicine.

ADVANCED TOPICS IN BIOMEDICAL RESEARCH

Symposium on Small Immunofluorescent Cells.
Fifty Years of the Ultracentrifuge.
Immunologic Control of Virus Associated with Tumors in Man.
International Conference on the Atmosphere.
Metabolic Products of Heme Catabolism.

Mr. CONTE. How do you distribute the proceedings of these conferences? To whom do you distribute them?

Dr. LEAVITT. The distribution of conference proceedings is determined in part by the subject and the estimated interested audience. Highly technical and specialized subjects have a limited distribution among the scientific community. Subjects of widespread interest and application are broadly distributed among health practitioners, educators, Federal health administrators and members of the U.S. Congress. The monograph series on preventive medicine falls into this latter category. In some instances popular editions for general public consumption are prepared to assure wider dissemination of conference proceedings.

WORLD HEALTH ORGANIZATION

Mr. CONTE. Your justification mentions the evaluation of World Health Organization personnel studying in the United States. Don't we also fund the World Health Organization's activities through our contribution to the United Nations? How much of your budget is devoted to this particular activity?

Dr. LEAVITT. By international agreement, multinational organizations are not permitted to work directly with Federal, State, and local

governmental agencies, except through the National Health Agency. Thus, the program referred to in our justification is a staff function performed as representatives of a member government in the WHO and the health professionals mentioned are totally funded by WHO.

Funds contained in this estimate support the salaries and related costs of seven individuals engaged in this activity, roughly $150,000.

Mr. CONTE. Thank you, that is all the questions I have.

Mr. FLOOD. Thank you, Doctor.

Dr. LEAVITT. Thank you, sir.

Justification of the Budget Estimates

Appropriation Estimate

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN THE HEALTH SCIENCES

For the John E. Fogarty International Center for Advanced Study in the Health Sciences, [$5,589,000] *$4,640,000*, of which not to exceed $500,000 shall be available for payment to the Gorgas Memorial Institute for maintenance and operation of the Gorgas Memorial Laboratory.

For the John E. Fogarty International Center for Advanced Study in the Health Sciences for the period July 1, 1976, through September 30, 1976, $1,135,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

Amounts Available for Obligation 1/

	1975 Estimate 2/	1976 Estimate
Appropriation	$5,589,000	$4,540,000
Comparative transfers to:		
"Office of International Health" (For US-USSR Exchange Program)	-137,000	---
"Office of the Director, NIH" (Transfer of funds for Public Affairs Reorganization)	-45,000	---
"Office of the Director, NIH" (Transfer of the Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	-1,000	---
Total obligations	5,406,000	4,540,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975-$200,000; 1976-$200,000.

2/ Excludes 1973 restorations in the amount of $185,000.

Summary of Changes

1975 Estimated obligations	$5,406,000
1976 Estimated obligations	4,540,000
Net change	-866,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in				
1. Within-grade pay increases	---	---	---	+14,000
2. Extra day of pay	---	---	---	+5,000
3. Federal Telecommunications System rate increases	---	---	---	+3,000
4. Service and supply rate increases	---	---	---	+4,000
5. Annualization of pay increases	---	---	---	+16,000
6. Annualization of health benefits	---	---	---	+3,000
7. Postage cost increase	---	---	---	+1,000
Total, increases	---	---	---	+46,000
Decreases:				
A. Built-in				
1. Payment to NIH Management Fund	---	---	---	-32,000
B. Program				
1. Scholars	---	2,000,000	---	-805,000
2. Research management and program services	51	2,906,000	-2	-75,000
Total, decreases	---	---	-2	-912,000
Total, net change	---	---	-2	-866,000

Explanation of Changes

Increases:

Built-in--The increases will provide: $14,000 for within-grade pay increases, $5,000 for an extra day of pay, $3,000 for Federal Telecommunications System rate increases, $4,000 for service and supply rate increases, $16,000 for annualization of pay increases, $3,000 for annualization of health benefits and $1,000 for postage rate increase.

Decreases:

A. Built-in--Payment to NIH Management Fund--The decrease of $32,000 is for reduced assessments for centrally furnished services.

B. Program

1. Scholars--A decrease of $805,000 will reduce the Scholars program by approximately 40 new awards.

2. Research management and program services--The reduction of $75,000 will reduce the International Center's Advanced Study Program, especially in the Preventive Medicine Studies.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
283	Gorgas Memorial Institute..	---	$500,000	---	$500,000	---	---
284	Scholars.....	---	2,000,000	---	1,195,000	---	-$805,000
286	Research management and program services.....	51	2,906,000	49	2,845,000	-2	-61,000
	Total, obligations.....	51	5,406,000	49	4,540,000	-2	-866,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions....	51	49	-2
Full-time equivalent of all other positions.....	8	8	---
Average number of all employees.....	57	57	---
Personnel compensation:			
Permanent positions.....	$1,037,000	$1,067,000	+$30,000
Positions other than permanent.....	94,000	95,000	+1,000
Other personnel compensation.....	17,000	17,000	---
Subtotal, personnel compensation...	1,148,000	1,179,000	+31,000
Personnel benefits.....	144,000	151,000	+7,000
Travel & transportation of persons.....	43,000	43,000	---
Transportation of things.....	6,000	6,000	---
Rent, communications & utilities.....	94,000	98,000	+4,000
Printing and reproduction.....	90,000	90,000	---
Other services			
Payment to NIH Management Fund.....	276,000	244,000	-32,000
Other.....	989,000	918,000	-71,000
Supplies and materials.....	88,000	88,000	---
Equipment.....	28,000	28,000	---
Grants, subsidies, and contributions...	2,500,000	1,695,000	-805,000
Total obligations by object.....	5,406,000	4,540,000	-866,000

Authorizing Legislation

	1976	
	Authorization	Appropriation Requested
Legislation		
Public Health Service Act		
Title III Part A - Research and Investigation in General (Section 301)	Indefinite	$4,040,000 1/
International Cooperation (Section 308)	Indefinite	
"An act to authorize a permanent annual appropriation for the maintenance and operation of the Gorgas Memorial" Public Law 70-350	$2,000,000	$500,000 1/

1/ Funding estimate only.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1968	$500,000	$500,000	$725,000	$500,000
1969	600,000	600,000	600,000	600,000
1970	3,460,000	2,954,000	2,954,000	2,954,000
1971	2,664,000	3,582,000	3,582,000	3,582,000
1972	3,369,000	3,813,000	4,338,000	4,338,000
1973	3,926,000	4,666,000	6,000,000	4,666,000 1/
1974	3,576,000	4,757,000	4,757,000	4,757,000
1975	4,601,000	4,201,000	5,817,000	5,406,000
1976	4,540,000			

1/ This appropriation was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate in the first vetoed bill.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1968	$500,000	$500,000	$725,000	$500,000
1969	600,000	600,000	600,000	600,000
1970	3,460,000	2,954,000	2,954,000	2,954,000
1971	2,664,000	3,582,000	3,582,000	3,582,000
1972	3,319,000	3,763,000	4,288,000	4,307,000
1973	4,545,000	4,666,000	6,000,000	4,666,000 1/
1974	3,586,000	4,767,000	4,767,000	4,767,000
1975	4,784,000	5,384,000	6,000,000	5,589,000
1976	4,540,000			

1/ This appropriation was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate in the first vetoed bill.

Justification

John E. Fogarty International Center
for Advanced Study in the Health Sciences

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	51	$1,292,000	49	$1,330,000	-2	+$38,000
Other expenses.....	---	4,114,000	---	3,210,000	---	-904,000
Total.....	51	5,406,000	49	4,540,000	-2	-866,000

General Statement

The John E. Fogarty International Center for Advanced Study in the Health Sciences was established to further the ideas and ideals of the late Congressman John E. Fogarty who envisioned an international center for research in biology and medicine dedicated to international cooperation and collaboration in the interests of the health of mankind. In following this mandate, the Center has initiated a number of programs which are designed to facilitate and expand the continuing effort of the National Institutes of Health and the Federal government to broaden the knowledge base of biomedical sciences.

Among the programs of the Center are its Advanced Study which encompasses specialized studies in preventive medicine, health care delivery, environmental health, examinations of selected aspects of medicine and health in the USSR and the People's Republic of China and comparative studies of health care systems of other countries; its Scholars programs, which include the Fogarty Scholars-in-Residence, the Senior International Health Fellowships and International Research Fellowships; and a number of staff support programs such as a Special Foreign Currency Program, International Visitors and Visiting Program and the programming of health professionals of other nations.

The Fogarty International Center is requesting $4,540,000 in 1976.

DHEW - National Institutes of Health

CROSSWALK - 1975 Column of 1976 President's Budget

INSTITUTE: John E. Fogarty International Center for Advanced Study in the Health Sciences
(in thousands of dollars)

Program \ Mechanism	Research Grants Specials Other	Other Direct Operations	Total
1. Gorgas Memorial Institute	$500		$500
2. Scholars		$2,000	2,000
3. Research Management and Program Services		2,906	2,906
Total Obligations.....	500	4,906	5,406

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DHEW - National Institutes of Health

CROSSWALK - 1976 Column of 1976 President's Budget

INSTITUTE: John E. Fogarty International Center for Advanced Study in the Health Sciences
(in thousands of dollars)

Program \ Mechanism	Research Grants Specials Other	Other Direct Operations	Total
1. Gorgas Memorial Institute	$500		$500
2. Scholars		$1,195	1,195
3. Research Management and Program Services		2,845	2,845
Total Obligations.....	500	4,040	4,540

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Mechanism

	1975 1/ Number	1975 1/ Amount	1976 Number	1976 Amount
Grants				
Special				
Gorgas Memorial Institute.....	1	$500,000	1	$500,000
Total Grants.....	1	500,000	1	500,000
Scholars.....	113	2,000,000	73	1,195,000
International Center.....	---	2,906,000	---	2,845,000
Total.....	---	5,406,000	---	4,540,000

1/ Excludes 1973 restorations in the amount of $185,000

Gorgas Memorial Institute

Authorizing Legislation: Public Law 70-350

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel Compensation and benefits.....	---	---	---	---	---	---
Other expenses.....	---	$500,000	---	$500,000	---	---
Total.....	---	500,000	---	500,000	---	---

Gorgas Memorial Institute

Introduction

The Gorgas Memorial Laboratory founded in 1921 and rendered functional in 1929 with direct support from the Congress of the United States, has the mission of conducting, assisting and encouraging "investigations in the sciences and arts of hygiene, medicine and surgery and allied subjects, in the nature and causes of disease and the methods of its prevention and treatment, and to make knowledge relating to these various subjects available for the protection of the health of the public and the improved treatment of disease and injury particularly as applied to tropical and preventive medicine." During the past forty-six years of scientific endeavor, the Gorgas Memorial Laboratory has placed major emphasis on the study of tropical infectious disease. Knowledge relating to the cause, natural history and control of malaria, Chagas' disease, leishmaniasis and vector-borne virus diseases has been greatly enhanced by the efforts of this research center. Incorporation of the Middle America Research Unit into the Gorgas Memorial Laboratory has increased the capability of this new educational and research complex and permits expansion of the scientific program to respond to a broader spectrum of health research needs of North and Latin America.

Program plans 1975 and 1976

The Fogarty International Center is responsible for the U.S. contribution to the Gorgas Memorial Laboratory and has been active in affairs of the Laboratory including review of scientific programs and promotion of Laboratory interests in the scientific community. As a result of hearings on a proposal to increase the authorization for this Laboratory, the Committee on Foreign Affairs has urged a more formal relationship between the Gorgas Memorial Institute and the Center to insure that the proposed expanded research and education program will be carefully coordinated with the overall Federal health research program. Embodied in the increased authorization is the creation of a regional health center dedicated to the study of a broad spectrum of major health problems of mutual interest to the United States and Latin America. These problems include diseases strongly influenced by environment, genetic and social factors and the ecologic derangements associated with industrial development.

Scholars

Authorizing Legislation: Public Health Service Act Title III Part A

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	---	---	---	---	---	---
Other expenses	---	$2,000,000	---	$1,195,000	---	-$805,000
Total	---	2,000,000	---	1,195,000	---	-805,000

Scholars

Fogarty Scholars-in-Residence

The Fogarty Scholars-in-Residence Program is the result of an effort to establish an environment wherein distinguished individuals from various parts of the world representing expertise in the broad biomedical field might convene for study, interaction, lecturing, etc. It was the intent to create an intellectual grouping with the thought in mind that such individuals as a group would provide inspiration to the intramural scientists with whom they might come in contact, and in addition, considerable benefit would be derived from their interaction among themselves plus the opportunity to indulge in writings, the initiation of all types of meetings from formal international conferences to workshop type conferences and seminars. The sum total of this involvement was expected to provide an impetus to the progress of biomedical research and in the final analysis, hasten the solution to many of the disease problems confronting us.

Intellectual stimulation is an intangible quantity and the concept of a scholars program is tied in with overall aims, objectives and capability of the parent organization. Cited below are selected examples of Scholars who have made a significant contribution to advancing the health sciences.

For many years, Professor John Edsall, the distinguished biochemist from Harvard, has made a number of scientific contributions to the field of physical biochemistry and, in particular, to proteins associated with the blood and blood problems. One of his earlier colleagues, and a distinguished scientist in his own right, Professor Jeffries Wyman, a physiologist at the Institute Regina Elena in Rome, Italy, cooperated very closely with Professor Edsall, and the two while Fogarty Scholars-in-Residence conducted a series of seminars involving senior staff of the NIH focusing on "allosteric interactions." These seminars have provided an insight into the basic knowledge which ultimately is needed to solve some of the more clinically oriented diseases associated with the blood.

Professor Ruggero Ceppellini of the Department of Genetics, University of Torino, Italy, who did a great deal of the original work in the blood groupings which are so well established in the research and clinical area. Professor Ceppellini, as an expert in immunogenetics, was attempting to shed light on the problem of tissue transplantation. He conducted and participated actively in conferences in this field, contributing significantly to the ideas and approaches. Hopefully, such contributions will ultimately aid in the resolution of the problem of tissue and organ transplants.

Fogarty Scholars Leo Sachs (Israel) and George Klein (Sweden), whose expertise is in the field of biochemistry of cancer, were deeply involved in collaborative research with a number of scientists within the NIH.

Senior International Fellowships

The Senior International Fellowships Program is designed to provide opportunities to outstanding faculty members at mid-career from U.S. schools of medicine, osteopathy, dentistry, and public health with demonstrated productive scholarship and recognized stature in their profession to go abroad to study and share their expertise. It is intended that this award be a career enhancing educational experience with mutual benefits to all involved. These research and public health scholarships are intended to:

1. increase the interchange of ideas of mutual interest between U.S. scholars in academic medicine and those of other nations of the world,

2. permit the exchange of the latest advances in a particular area of medicine, both basic and clinical,

3. permit participation in the contribution to on-going research in the medical sciences or in science areas related to medicine, and

4. improve the academic, research and/or clinical biomedical potential of the U.S. medical institution.

This Program, announced mid-year of fiscal 1974, has had an enthusiastic response from the U.S. scientific community. Without regard to the very limited time frame within which to qualify for 1975 awards, inquiries have been received from over 400 individuals from 45 states. In addition, at this writing, applications from 25 faculty members representing 21 universities have been received for consideration.

International Research Fellowships

The International Research Fellowships Program offers a unique opportunity for the sharing of scientific information on an international basis by providing an opportunity to foreign investigators to work for a period of a year or two in collaboration with, and in the laboratories of, American colleagues in the United States. This program provides U.S. scientists access to the ideas of vigorous young investigators with stimulating and different viewpoints. In addition, since Fellows return to do independent research in their home countries, a basis is provided for the future collaboration between investigators here and those in different environmental settings.

Program Plans in 1975 and 1976

The Fogarty International Center will continue to seek outstanding individuals for invitation and participation in the Scholars Program. The Senior International Health Program although only recently initiated and despite very rigid criteria has had an outstanding response. Hundreds of inquiries have been received with firm responses and applications from twenty-five highly qualified individuals. With the additional lead time, a much greater response is anticipated. Nominations from national committees of other countries for the International Research Fellowship Program are always in excess of the opportunity for awards. We will continue to select only the very highest quality applicants.

Research Management and Program Services

Authorizing Legislation: Public Health Service Act Title III Part A

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	51	$1,292,000	49	$1,330,000	-2	+$38,000
Other expenses.....	---	1,614,000	---	1,515,000	---	-99,000
Total	51	2,906,000	49	2,845,000	-2	-61,000

Research Management and Program Services

This activity supports the Fogarty International Center programs of advanced studies, as well as the scientific, administrative and clerical staffs responsible for the overall coordination and administration of the total activities of the Center.

Program Plans for 1975 and 1976

The advanced study program is accomplished through its conferences and seminars which annually invites hundreds of individuals to participate in the review and discussion of major biomedical issues. During the past few years, over 50 conferences, seminars or workshops have been held and proceedings have been published and distributed.

Another element of the advanced study program is the Geographic Health Studies which seeks to improve the nation's health by insuring that useful and pertinent knowledge developed in foreign countries is made available for consideration by U.S. medical and professional personnel. During the past few years, the Center has utilized the services of dozens of world experts to examine research, education and health care in the Soviet Union and the Peoples Republic of China. Comparative studies of the health services of other countries are also underway.

The Fogarty International Center has the coordinating and policy formulation function and operating responsibility for the NIH Special Foreign Currency Program which is supported with an allotment of funds from the appropriation "Scientific Activities Overseas" managed by the Office of International Health, Office of the Secretary, DHEW.

The International Visitors Center provides an opportunity to visitors for discussion of international biomedical problems with professional staff and for the arrangement of appropriate contacts between such visitors and the Fogarty International Center and NIH staff members.

The International Education Program is responsible for arranging of professional programs for, providing supervision and consultation to, and maintaining on-going evaluation of the training experiences of World Health Organization supported medical and allied health professionals studying in the United States.

The 1976 budget provides for a net decrease of $61,000. This includes increases of $46,000 for built-in items: $14,000 for within-grade pay increases; $5,000 for an extra day of pay; $3,000 for Federal Telecommunications System rate increases; $4,000 for service and supply rate increases; $16,000 for annualization of pay increases; $3,000 for annualization of health benefits; and $1,000 for postage rate increase. Payments to the NIH Management Fund will decrease by $32,000. A program decrease of $75,000 will be made in the Advanced Study Program in the area of Preventive Medicine.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Program Purpose and Accomplishments

Activity: Research grants (Public Law 70-350)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$500,000	$2,000,000	---	$500,000

Purpose: This grant provides the legislatively authorized U.S. contribution for the operation and maintenance of the Gorgas Memorial Laboratory now comprising the merged facilities of the former Middle America Research Unit and The Gorgas Memorial Laboratory. The purpose of this institution is to conduct research on tropical diseases of public health importance to the United States and Latin America, to provide guidance for the application of research findings to preventive and therapeutic ends and to provide education opportunities for students of tropical medicine.

Accomplishments in 1975: During fiscal year 1975 The Gorgas Memorial Laboratory continued research on malaria, trypanosomiasis, leishmaniasis, bacterial diarrheas and arboviruses of public health importance. Major accomplishments include the adaptation of human malaria parasites to indigenous simian species and the initiation of experimental chemotherapy in these hosts; the recognition of the major insect vector of trypanosomiasis in virgin forest; new mammalian hosts for the three species of leishmania in Panama; further study of ecologic derangement in the Bayano River impoundment area; attenuation of a potential vaccine strain of Bolivian Hemorrhagic Fever virus; identification of in-vitro markers of VEE virus isolates of differing virulence; six new viruses from phlebotomine flies; serologic evidence of dengue virus activity in man; and serologic evidence of recurrence of sylvan yellow fever. Training of postdoctoral candidates continued under the aegis of university exchange and military medicine programs.

Objectives in 1976: The Gorgas Memorial Laboratory proposes to exploit fully current findings in experimental malaria in simian models, studies of immunity in human infection with trypanosomes and leishmania, further evaluation of attenuated vaccine candidates of BHF virus and studies of ecology of VEE, sand fly viruses and yellow fever. Current activities include major efforts to contain recurrent human yellow fever and attendant risk of urban outbreaks.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Program Purpose and Accomplishments

Activity: Scholars (Public Health Service Act Title III Part A)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$2,000,000	Indefinite	---	$1,195,000

Purpose: The Fogarty Scholars-in-Residence Program provides outstanding scientists and other scholars the opportunity to focus their attention on broad aspects of important issues raised by the finding of modern biomedical research. While in residence at the Center the scholars are encouraged by group interaction to attack broad problems, the solutions to which require an interdisciplinary approach or whose solution lies beyond the knowledge of a single individual. Fogarty Scholars-in-Residence through the unique environment at NIH have an unusual opportunity to interact with a large number of intramural staff scientists in discussions of various problems within their specific discipline, such as biochemistry, physiology, etc., particularly as they relate to cancer and cardiovascular research.

The International Postdoctoral Fellowships Program offers a unique opportunity for the sharing of scientific information on an international basis by permitting foreign investigators to work for a period of a year or two in collaboration with, and in the laboratories of, American colleagues in the United States. This program provides U. S. scientists access to the ideas of vigorous young investigators with stimulating and different viewpoints. In addition, since Fellows return to do independent research in their home countries, a basis is provided for the future collaboration between investigators here and those in different environmental settings.

The Senior International Fellowship Program provides opportunities to outstanding faculty members at mid-career from U. S. schools of medicine, osteopathy, dentistry and public health with demonstrated productive scholarship and recognized stature in their profession to go abroad to study and share their expertise. This Program is intended to be a career enhancing educational experience with mutual benefits to all involved.

Accomplishments in 1975: In 1975, 113 awards were made to individuals in order to engage in collaborative research with American scientists on health problems of mutual interest and to advance the basic knowledge in the biomedical sciences, in such areas as molecular biology, cell biology, genetics, neurophysiology, endocrinology and others.

Objectives in 1976: In 1976, 73 awards will be made to applicants whose research proposals will have a direct effect upon research in the disciplines such as cell biology, biochemistry, physiology and other biomedical fields as they may apply to cancer, cardiovascular diseases, neurological diseases, medical genetics, metabolic diseases and others.

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Program Purpose and Accomplishments

Activity: Research management and program services (Public Health Service Act Title III Part A)

1975 Estimate		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
51	$2,906,000	Indefinite	49	$2,845,000

Purpose: The John E. Fogarty International Center for Advanced Study in the Health Sciences is designed to facilitate and expand the continuing effort of the National Institutes of Health and the United States Government to broaden the knowledge base of the biomedical sciences. The Center serves as the focal point for the international activities of the National Institutes of Health. The Center also is responsible for the administration of a number of international programs such as International Fellowships, Scholars-in-Residence, Advanced Study, International Visitors Center, Special Foreign Currency, and programming of health professionals of other nations.

Accomplishments in 1975: Partial results of the Fogarty Center sponsored studies on various aspects of preventive medicine will be published in 1975. This timely subject has received increased attention during the past several years and these publications will contribute to the knowledge base for further examination. Other studies, particularly studies of medicine and public health in the Soviet Union and the People's Republic of China have resulted in publications which are being added to the curriculum of Schools of Medicine and Public Health.

Objectives in 1976: Continued activity in the advanced study area, either through individual studies or conferences, workshops and seminars, will permit further analyses and comparative studies of medicine and public health and the exchange of scientific and biomedical knowledge including additional results of preventive medicine studies.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced Study in the Health Sciences

Amounts Available for Obligation 1/

	1976 Estimate	Interim Period
Appropriation	$4,540,000	$1,135,000
Total, obligations	4,540,000	1,135,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976-$200,000; Interim Period-$50,000.

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Gorgas Memorial Institute	---	$500,000	---	$125,000
Scholars	---	1,195,000	---	299,000
Research management and program services	49	2,845,000	49	711,000
Total, obligations	49	4,540,000	49	1,135,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	49	49
Full-time equivalent of all other positions	8	2
Average number of all employees	57	14
Personnel compensation:		
Permanent positions	$1,067,000	$267,000
Positions other than permanent	95,000	24,000
Other personnel compensation	17,000	4,000
Subtotal, personnel compensation	1,179,000	295,000
Personnel benefits	151,000	38,000
Travel & transportation of persons	43,000	11,000
Transportation of things	6,000	1,000
Rent, communications & utilities	98,000	24,000
Printing and reproduction	90,000	23,000
Other services:		
Payment to NIH Management Fund	244,000	61,000
Other	918,000	229,000
Supplies and materials	88,000	22,000
Equipment	28,000	7,000
Grants, subsidies, and contributions	1,695,000	424,000
Total obligations by object	4,540,000	1,135,000

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the John E. Fogarty International Center for Advanced Study in the Health Services consistent with the 1976 estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

NATIONAL LIBRARY OF MEDICINE

WITNESSES

DR. MARTIN M. CUMMINGS, DIRECTOR
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
MELVIN S. DAY, DEPUTY DIRECTOR, NATIONAL LIBRARY OF MEDICINE
KENT A. SMITH, ASSISTANT DIRECTOR FOR ADMINISTRATION, NATIONAL LIBRARY OF MEDICINE
FRANK B. POH, FINANCIAL MANAGEMENT OFFICER, NATIONAL LIBRARY OF MEDICINE
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. Now we have the National Library of Medicine.

The presentation will be made by Dr. Martin M. Cummings, the Director. We will include your biographical sketch in the record, Doctor, and is there anybody we don't know that you have with you here this morning?

[The biographical sketches follow:]

Name, Martin Marc Cummings; position, Director, National Library of Medicine; birthplace and date, Camden, N.J., September 7, 1920; education, B.S., Bucknell University, 1941, M.D., Duke University, 1944.

Experience: Present, Director, National Library of Medicine.

1963–64, Associate Director for Research Grants, National Institutes of Health.

1961–63, Chief, Office of International Research, National Institutes of Health.

1959–61, professor of microbiology and chairman, department of microbiology, University of Oklahoma School of Medicine.

1953–59, Director, Research Services, Veterans Administration Central Office.

1953–59, special lecturer in microbiology, George Washington University School of Medicine.

1953, associate professor of bacteriology, Emory University.

1949–53, Chief, Tuberculosis Research Laboratory, Veterans Administration Hospital of Atlanta.

1948–53, instructor through associate professor of medicine, Emory University.

1947–49, Director, Tuberculosis Evaluation Laboratory, Communicable Disease Center, U.S. Public Health Service.

1945–49, assistant resident, Boston Marine Hospital.

1944–45, intern, Boston Hospital.

1942–1944, U.S. Army, private first class.

Association memberships: American Academy of Microbiology, Inc.; American Board of Microbiology; American Federation for Clinical Research (Emeritus); American Society for Clinical Investigation (Emeritus); Association for American Medical Colleges; Medical Library Association; Society of Sigma XI; American Clinical and Climatological Association; American Society for the History of Medicine; Board of Directors, Gorgas Memorial Foundation; American Documentation Institute; Association of Research Libraries; Society of Medical Administrators.

Special awards, citations, or publications: Veterans Administration Exceptional Service Medal; DHEW Superior Service Award; DHEW Distinguished Service Award; Honorary Doctor of Science, Bucknell University, 1969; Distinguished Alumnus Award, Duke University; Honorary Doctor of Science, University of Nebraska, 1971; Honorary Doctor of Science, Emory University, 1971; Honorary Doctor of Humane Letters, Georgetown University, 1971; Honorary Members, Alpha Omega Alpha; Honorary Doctor of Medicine, Karolinska Institute, Stockholm, Sweden, 1972; Honorary Fellowship, College of Physicians, Philadelphia, 1973; Rockefeller Public Service Award, 1973.

Name, Melvin Sherman Day; position, Deputy Director, National Library of Medicine; birthplace and date, Lewiston, Maine, January 22, 1923; education, B.S., Bates College, Lewiston, Maine, 1943.

Experience:

Present, Deputy Director, National Library of Medicine.

1971–72, Head, Office of Science Information Service, National Science Foundation.

1966–71, Deputy Assistant Administrator for Technology Utilization, NASA headquarters.

1962–66, Director, Scientific and Technical Information Division, NASA Headquarters.

1960–62, Deputy Director, Office of Technical Information and Education, NASA Headquarters.

1958–60, Director, Division of Technical Information, AEC.

1956–58, Chief, Technical Information Extension, AEC.

1955–56, Assistant Chief, Technical Information Extension, AEC.

1952–55, Operations Officer, Technical Information Services, AEC.

1948–52, Physical Science Information Editor, Technical Information Service, AEC.

1946–48, Chemist, Technical Information Division, AEC.

1944–46, U.S. Army Corps of Engineers and served as laboratory foreman (chemist), U.S. Army, Eastman Kodak Corp.

1943–44, Chemist, Metal Hydrides, Inc.

Association memberships: American Association for the Advancement of Science; New York Academy of Sciences; American Chemical Society; American Society of Information Science; Special Libraries Association; Medical Libary Association.

Special awards, citations or publications: NASA Exceptional Service Medal Sustained Superior Performance Award, AEC.

Name, Kent Ashton Smith; position, Assistant Director for Administration, National Library of Medicine; birthplace and date, Boston, Mass., September 3, 1938; education, B.A., Hobart College, 1960, M.P.A., Cornell University 1962.

Experience:

Present, Assistant Director for Administration, National Library of Medicine.

1968–71, Executive Officer, Division of Research Resources.

1968, Acting Executive Officer, Division of Research Facilities and Resources.

1967–68, Assistant Executive Officer, Division of Research Facilities and Resources.

1965–67, Administrative Officer, Division of Research Facilities and Resources.

1962–65, Management Analyst, Office of the Secretary, Office of Management Policy.

Association memberships: Sigma Phi Society, Society for Advancement of Management; American Society for Public Administration.

Name, Frank Benedict Poh; position, Financial Management Officer, National Library of Medicine; birthplace and date, Washington, D.C., April 5, 1931; education, B.B.A., Southeastern University, 1960, M.B.A., Southeastern University, 1965.

Experience:

Present, Financial Management Officer, National Library of Medicine.

1969–73, Budget Officer, National Library of Medicine.

1967–68, Grants Management Officer, Division of Research Facilities and Resources.

1966–67, Systems Accounting Officer, Department of the Army.

1962–66, business manager, Eastern area, Chrysler Corp.

1960–62, controller, P. J. Nee Co.

1958–60, director of finance, Heppner Engineering Co.

1955–58, office manager, Wissinger Chevrolet Co.

1949–55, U.S. Marine Corps., sergeant.

Association memberships: Sigma Alpha Sigma; American Society of Public Accountants; Federal Government Accountants Association; American Society for Public Administration.

Special awards, citations, or publications: DHEW Quality Performance Award, 1972.

Dr. CUMMINGS. I believe the committee previously has met Mr. Smith and Mr. Day, senior members of my staff.

Mr. FLOOD. You have a statement. How do you want to handle that?

Dr. CUMMINGS. With your permission, I would like to read it and handle any questions you have.

Mr. FLOOD. Please do.

OPENING STATEMENT

Dr. CUMMINGS. Mr. Chairman and members of the committee, as our Nation prepares for its bicentennial observance the National Library of Medicine enters its 140th year. NLM traces its origin back to 1836 when a small collection of medical books and journals were acquired and located in the office of the Army Surgeon General. Today the National Library of Medicine with its 1,500,000-volume collection serves as the world's largest research library in a single scientific and professional field.

Mr. FLOOD. This history and service, I am sure, is not generally known. It is simply not known; is it?

Dr. CUMMINGS. Unfortunately, it isn't generally known to the public. I believe the medical community, however, has insight into this.

Mr. FLOOD. Yes, I meant to the general public.

Dr. CUMMINGS. It continues to perform its legislative mandate to acquire, organize, and disseminate printed and audiovisual informational materials in the biomedical sciences. Index Medicus, which had its genesis in 1879, still serves as an invaluable tool to the Nation's physicians and scientists and is sold to more than 6,000 institutions throughout the world.

Mr. FLOOD. What is Index Medicus?

Dr. CUMMINGS. Index Medicus is the listing of all the world's medical literature as it appears monthly. It announces the articles published, the author's name and citations that may be used to reach this literature.

In order to effectively and efficiently provide timely information services to the entire health community, a national biomedical communications network utilizing the latest in technological advances has been developed and is continually being enhanced.

BIBLIOGRAPHIC SERVICES

One of the prime tools of today's technology is the computer, and NLM has pioneered in its use for bibliographic information storage and retrieval. In 1964 NLM introduced the computer-based Medlars I system, which permitted both computerized production of Index Medicus and automated searches of the entire bibliographic data base by health professionals.

I am pleased to inform this committee that in January of this year NLM implemented its new information system, Medlars II. This milestone culminates an intensive 3½ year effort to develop a more sophisticated bibliographic processing system which employs

the most modern third generation computer technology. Medlars II is installed on NLM's newly expanded computer configuration which allows the extension of our services to the entire health community. In addition to the increased speed and capacity to serve online users, Medlars II makes it possible to generate and photocompose new bibliographic publications, and to provide more flexible search formulations and information retrieval.

Health professionals at over 300 institutions in this country and abroad can now directly interact with the computer through terminals which access the Medlars data base containing citations and abstracts of relevant medical literature. Approximately 300,000 searches were performed last year. In order to moderate the growth of Medline and to cover all of its communications costs, we are increasing our user charges moderately. Under a new agreement with the Commerce Department's National Technical Information Service, that agency will collect fees to offset the costs of making online data bases accessible equally to all parts of the country. Any excess collections will be returned to the U.S. Treasury.

Obtaining citations to the relevant literature is only the first step for the health professional seeking information. He must then obtain the literature for study. Few health science libraries subscribe to all of the 3,000 journals which NLM indexes for Medline, but they can locate and receive copies of literature needed by their patrons via an NLM-supported interlibrary loan network. Although NLM resource grants help many smaller medical libraries purchase the basic literature most frequently consulted by practitioners, a local hospital library still may not have the particular article or book needed. In that case, the institution may request an interlibrary loan from a larger medical library in its region. NLM supports 10 such Regional Medical Libraries throughout the country, each responsible for providing interlibrary loans and Medline services in a defined geographic area.

NLM itself, with the most comprehensive collection of health science literature in the world, backs up the entire network and attempts to supply materials unavailable from these primary sources. It also serves as the Regional Medical Library for the Mid-Atlantic Region.

CANCERLINE

Increasingly, other health agencies are benefiting from the communications expertise which NLM has developed over the years. Using NLM's computer and international telecommunications network, for example, the National Cancer Institute is providing cancer-related citations and abstracts for an online data base that is now available at each of the numerous Medline centers. In 1975 over 18,000 carcinogenesis abstracts will be added to this data base (called Cancerline), and the number of abstracts is expected to increase by about 10,000 each year. NLM's considerable experience with online systems allows it to make a significant contribution to worldwide cancer research and treatment.

MEDICAL LIBRARY ASSISTANCE

I have already referred to NLM's regional medical library and resource grants programs. These are part of the activities originally authorized by the Medical Library Assistance Act of 1965. Together with grants for training, special scientific projects, research, and bio-

medical publications, these programs continue to support a coordinated approach to the problem of assuring equal and efficient access to biomedical information in all parts of the country.

COPYRIGHT SUIT

Before turning to other programs of the NLM, I would like to inform the committee of the status of the copyright suit against the National Library of Medicine and the NIH Library. As you know, a publisher of some biomedical journals alleged that the NLM and the NIH Library had infringed their copyright by providing photocopies of journal articles to library patrons. The U.S. Court of Claims found in favor of the Government and in February 1974, the U.S. Supreme Court sustained their decision. This outcome has been enthusiastically welcomed by the Nation's library and educational community. With this ruling all interest in copyright is again focused on the congressional efforts to produce a new copyright law.

AUDIOVISUAL SERVICES

In 1967 the National Medical Audiovisual Center (NMAC) in Atlanta, Ga., which is responsible for developing a large and diverse collection of health science audiovisuals, was transferred to the National Library of Medicine. NMAC is much more than a repository; it is actively developing programs for applying audiovisual technology to the problem of training sufficient health manpower to meet present and future needs. With the assistance of special panels of educators and biomedical specialists NMAC identifies, produces, collects, and evaluates mediated instructional materials appropriate for the basic and continuing education of health professionals. Instructional materials judged to be sound in content and of high technical quality will become part of a new computerized online retrieval system analogous to Medline and available across the country through the NLM communications network. Called Avline, it enables a user to identify audiovisuals by subject matter. It also provides information on where audiovisuals may be obtained and on their content, quality, and intended audience. As with journal articles, however, identifying the needed material is only the first step. NMAC also makes loans of motion pictures and videotapes to schools of the health professions and consults with them on ways to utilize audiovisuals more effectively.

In fiscal year 1975 NMAC will loan approximately 65,000 films and videotapes to the health community. They will be viewed by more than a million students and practitioners in the health sciences.

NMAC works closely with the Bureau of Health Resources Development of the Health Resources Administration (HRA) in the production of nonprint teaching materials for the health community. One joint effort has produced instructional materials in operative dentistry and they are now in use in most dental schools.

TOXICOLOGY INFORMATION

NLM's toxicology information program is responsible for developing and operating a computer-based toxicology information storage and retrieval system. It also provides publications, other information

packages, and literature services to satisfy the rapidly growing needs of other Federal agencies, universities, and industrial firms for toxicology information. One of the ways in which the program meets these needs is through the development of Toxline—a computer-based information retrieval system which contains information about pharmacology, toxicology, environmetnal pollution, and occupational health and safety. Like Medline it is accessible via terminals which connect users to the NLM computer. The computerized data base, which currently includes over 350,000 searchable citations, index terms, and abstracts of the published literature, brings together information from diverse sources which otherwise would be much less accessible. In fiscal year 1976 the file will be enriched with additional references in areas of special significance, such as chemicals causing birth defects and cancer.

LISTER HILL NATIONAL CENTER FOR BIOMEDICAL COMMUNICATIONS

The Lister Hill National Center for Biomedical Communications is the research and development arm of the Library. It coordinates closely with other Federal agencies as well as the medical community. Its orientation is to seek to expand the horizons of problem solving in the areas of health care delivery, education and research through the use of communications technology.

One example of such an approach is to increase the effectiveness of health care delivery in isolated communities by establishing communications with sophisticated backup health facilities. Initially, this was done through voice communications where, for example, in Alaska it was shown that interference-free voice communication via the ATS 1 satellite was of great help in decisionmaking both with regard to support for onsite treatment by health aides, and for determining the necessity of evacuating patients to more comprehensive health facilities.

Experiments have been undertaken to determine to what extent these benefits may be increased through the introduction of 2-way video transmission as well as physiological monitoring through the use of the ATS 6 satellite. In this experiment it is possible both to see the patient, and examine his physiological data (e.g. electrocardiogram) as well as monitor his vital signs.

Additionally, experiments have been undertaken to determine the effectiveness of long range consultation particularly in the areas of psychiatry and dermatology via two-way communications systems. Thus, both in the Pacific Northwest via the ATS 6 satellite, and in the Northeast via a terrestrial interactive TV network, it is possible for a consultant to "examine" and treat a patient many miles away.

In a similar fashion, the role of communications technology in both undergraduate and postgraduate medical education is being studied. The WAMI program in the Pacific Northwest represents an experiment in decentralization in undergraduate medical education.

Mr. FLOOD. You had better translate WAMI.

Dr. CUMMINGS. That is an acronym for Washington, Alaska, Montana, and Idaho. It is a consortium of four States in education and health programs. It is a very exciting educational program, Mr. Chairman. We believe that experiments of this nature may help solve the problem of training physicians in States whose population densities cannot support medical schools, such as Wyoming and Idaho.

Interactive communications systems make it possible to extend and integrate faculties in geographically distant areas into a cohesive and complementary whole. Using satellite communications, students receive basic science instruction at the University of Alaska, and clinical training in rural parts of the State of Washington. They are instructed by the faculty of the University of Washington School of Medicine, in Seattle. In these experiments the Lister Hill Center has been working closely with the Health Resources Administration.

The Lister Hill Center is also participating with the Health Services Administration in creating a continuing medical education program for physicians in the newly established National Health Service Corps. One objective of the program is to reduce the degree of professional isolation experienced by these physicians, and hopefully to encourage them to remain in place and continue participation in these medically underserved areas.

Together with the Health Resources Administration, efforts are being made to provide information to such practitioners in a timely and effective manner. An additional concern is to determine what information is most valuable both from the point of view of alleviating their sense of isolation and in contributing to improvement of the quality of care. The Lister Hill Center acts as a forum, a coordinator, and an agent for initial funding of exploratory and demonstration projects. In these demonstrations it is consistently cognizant of the necessity to plan for the ultimate operational support should they prove successful. The Lister Hill Center works toward the evolution of local self-sufficiency if possible, and other agency support where necessary. The Lister Hill Center itself does not support proved operating systems. To carry out these services, Mr. Chairman, the budget request for the National Library of Medicine for 1976 is $28,815,000. I shall be pleased to try to answer any questions and supply additional information which you may desire for the record.

LISTER HILL CENTER FACILITY

Mr. FLOOD. Doctor, last year you told us that the architectural and the engineering drawings for the Lister Hill building would be completed by the end of calendar year 1974. Do you have a finalized set of drawings?

You know that this committee from the beginning has been very much concerned right along about the Lister Hill building, for Lister was an old friend of ours. How about that?

Dr. CUMMINGS. I regret that my estimates last year were off by some 3 or 4 months, but I have been assured, Mr. Chairman, that the architects have completed design of this facility and that they will be delivered to NIH next month.

Mr. FLOOD. I hope so. We want to see that thing underway. What will it cost to construct that building?

Dr. CUMMINGS. The present estimates of cost for the Lister Hill facility without parking arrangements is about $20 million.

Mr. FLOOD. What is the estimated cost per square foot?

Dr. CUMMINGS. I believe the estimated cost per square foot is between $95 and $100.

Mr. FLOOD. Is there any money requested in the NIH budget for the construction of the Lister Hill building?

Dr. CUMMINGS. There is no money in the President's budget for this facility.

Mr. FLOOD. If we delay the cost of this building another year, what is your best estimate of the cost?

Dr. CUMMINGS. I am advised that the cost of construction goes up at a rate of about 10 to 12 percent a year. That would then raise the cost of the Lister Hill facility to a level of about $23 million or $24 million.

Mr. FLOOD. In view of the fact that the fiscal year 1976 budget does not contain funds for this facility, the Congress can only appropriate a portion of the total cost of the project, could this project be subdivided or phased in any way? It is about time we get down to business on this thing.

Dr. CUMMINGS. Mr. Chairman, this question was raised last year by the Senate Subcommittee on Appropriations, and we have recently reexamined this issue. I am advised that the most desirable method of proceeding is to authorize the construction for this facility with a 3-year phasing of this appropriation.

Such a plan would provide about 30 percent of the total cost within the first year or $5.7 million. An additional 50 percent of the cost during the second year would be needed or about $9¼ million, with the remaining 20 percent for the complex in the third year.

Mr. FLOOD. If we funded only the first part of this construction what would be your estimate of cost?

Dr. CUMMINGS. On a 3-year base situation it would require about $5.7 million. If the building were phased on a 2-year basis, it would be about $10 million for the first and $10 million for the second phase.

Mr. FLOOD. It is about time this thing is off the ground.

Dr. CUMMINGS. It is 7 or 8 years since the joint resolution of the Senate and House called for the creation of this facility.

EXPERIMENTAL COMMUNICATION NETWORKS

Mr. FLOOD. Last year we talked a lot, we had a very exciting talk about the satellite experiments which provide the live television consultation between the physicians in the Indian Health Service Hospital and health aides at several of these remote clinics in Alaska.

Have these experiments proved to be effective?

Dr. CUMMINGS. Yes, sir. In my view those experiments have not only proven to be interesting, but have in fact proved to have practical utility. I have been advised, for example, that on the basis of the success of these demonstrations that the State of Alaska is considering developing a statewide communication system based on satellites. The efficiency is quite impressive.

Mr. FLOOD. Do you have plans to expand these experiments to include other geographical areas of the country?

Dr. CUMMINGS. Yes, sir.

With the present experiment using the more sophisticated satellite known as ATS–6, we are now able to cover the Rocky Mountain areas and a small part of the Southwestern States as well as some of the U.S. trust territories in the Pacific. In the future we look forward to working with the Canadian telecommunications apparatus that would give us the opportunity to blanket larger portions of our Nation, in-

cluding Appalachia and other medically underserved components of our country.

Mr. FLOOD. For what period of time do you support these experimental communication networks?

Dr. CUMMINGS. Our experience so far suggests that it takes between 5 and 6 years to mount a program, to test it, and to evaluate its efficiency. That is the experience we have had to date.

We then withdraw from the basic support and try to turn it over to the local community.

Mr. FLOOD. Who will pick up the support of these communication networks if you withdraw your financial support?

Dr. CUMMINGS. Hopefully the medical community itself, States and local governments which may be interested, will provide the support as we gradually withdraw. We do not cut off precipitously, I should point out. We try to phase this out and we try to maintain a relationship with the local institutions so that they are actually prepared for this.

Mr. FLOOD. You mention in your opening statement that the role of the communication technology in both undergraduate and postgraduate medical education is being studied. You also mentioned WAMI, an experiment up in the Pacific Northwest. Can you tell us more about your experiment and your other work in this area?

Dr. CUMMINGS. I can tell you that the students and the faculty at the University of Washington in Seattle both report that the teaching of basic science can take place through interactive communications, that the students who are physically located in Fairbanks, as members of the class of the University of Washington are doing as well as those students who are taking the courses on campus. I believe the strategy here is to have these students stay in place after they graduate so that students who come from remote places in Alaska and taste Seattle don't decide to live in Seattle but recognize they can maintain medical contact even when they return to their point of origin.

Mr. FLOOD. There is a lot of talk and interest all through the country from small town colleges about tying into the larger metropolitan area medical universities and medical colleges in these combined courses. There are 6-year courses; 2 years at the local small college, and 2 years at the big medical college downtown and back to the small town for 2 more years getting an MD in these combined courses, tying in the hospitals, et cetera.

Is that part of your program? Do you help in these things?

Dr. CUMMINGS. No, sir. That is not part of our program. I believe the Bureau of Health Resources Development of HRA would be more involved with those combined activities. Where such a program requires communication experitise for success, HRA has called upon us in developing this kind of linkage.

Mr. FLOOD. I can see where telecommunications would be important for taking back the lectures of the university or the college operations perhaps even on patients, taking the whole thing back to the colleges, to the classrooms and the hospitals of the surrounding community.

In many ways that would be beneficial for the interns and paramedics.

Dr. CUMMINGS. I believe there are many activities along the lines of your description that are now underway.

Mr. FLOOD. All the Institute directors who have testified here so far have placed a great amount of importance on the transmitting of new knowledge discovered in the laboratory to the practicing physician. How does the Lister Hill Center achieve that kind of objective?

Dr. CUMMINGS. I think the problem of dissemination of research results into clinical application is a prime example of the programmatic interest of the Lister Hill Center. We have each year since the Center was developed maintained a structure through which we work with professional societies, learning of their needs in continuing education. We try to provide new communication modalities for the physician to get access to research information.

Now this is done, of course, in many different ways. A physician can go to meetings if he can close up his office. As you know, many solo practitioners cannot do that. We are now trying to bring the information to his office, to his clinic and to his home.

Mr. FLOOD. What kind of practitioner?

Dr. CUMMINGS. The general practitioner.

Mr. FLOOD. You used another term.

Dr. CUMMINGS. I said solo. He practices alone. Often he cannot afford to close his office to go to medical meetings to get this knowledge.

We are trying to bring it to him through printed word and audiovisual forms and now through direct contact between him and an expert at a great medical center.

Mr. FLOOD. How do the Institutes at NIH use this center to disseminate new technology to the practicing physician?

Dr. CUMMINGS. As an example, through our bibliographic resources we tell the practitioner what has just come off the press in research results.

We do this through a special publication called Abridged Index Medicus. It lists only the practical clinical findings. It does not have the exotic foreign language literature. Each month this reaches the practitioner and he can scan it and find the latest publications in diabetes, hypertension, carcinoma of the breast, et cetera. This is one way we try to serve him. Also, we put library resources in his community hospital where he spends a good bit of his time. We consider the community hospital, Mr. Chairman, as the underdeveloped base of continuing education for health professionals. That is why the small resource grants, $3,000, $4,000, or $5,000, are critically important to giving him information in his hometown so he does not have to go great distances to seek it out.

Mr. FLOOD. This sounds great.

We have also heard a lot of testimony in the past weeks about educating the general public. That is a good idea, educating them about maintaining good health. What role does the Lister Hill Center play in that kind of program?

Dr. CUMMINGS. The Lister Hill Center and indeed the library I must confess, has not developed an active program in providing consumer education or public education.

We anticipate that the Center in Atlanta, the Center for Disease Control, which I believe has this mission added to its responsibilities, will assume that important task. However, the audiovisual materials

that we provide are shared with them so that they can be used by patients and the public in learning how to take care of their general health problems. But we do not have that as a primary responsibility.

USER CHARGES

Mr. Flood. In your opening statement, you made quite a thing about this.

You are increasing your user charges moderately, you say. For what services do you apply the user charge?

Dr. Cummings. We charge a user fee for every specialized service we provide. We are doing this, we believe, at the request of this committee and the Office of Management and Budget. We think it is a useful concept, that the user pay at least the cost of reaching the central data base at NLM. We do not charge him for the cost of development of the information for which you appropriate funds or for the organization of this material. But anything that connects him to the library requires a communication cost which he pays.

Mr. Flood. How much do you collect annually on a user charge?

Dr. Cummings. The unit rate is $8 an hour. The physician or scientist can make four or five searches in an hour. Mr. Smith will answer.

Mr. Smith. It will run approximately $400,000 this year. It will be about $800,000 next year with the charges going up.

Mr. Flood. Does that all go back to the general Treasury?

Dr. Cummings. It is used to pay the communication cost for the network.

Mr. Smith. Any excess goes back to the Treasury.

Dr. Cummings. We are going to raise that fee to $15 an hour during prime time, because like the telephone system we are getting overburdened during peak hours. Our intention, Mr. Chairman, is to take whatever excess collection there may be and return that to the Treasury. But so far we have had no money in this category.

Mr. Flood. Do you plan in the future to apply a user charge to a much greater number of the services that you now provide to the medical and industrial community, too?

Dr. Cummings. We intend to provide a user charge for any specialized technical service but none for traditional library service like lending and borrowing, but anything that requires specialized computer service we will charge for.

Mr. Flood. To the medical community and the industrial community.

Dr. Cummings. Yes, there will be an equal charge to any member of the health community.

Mr. Flood. What effect will the increase in the user charge have on the utilization of your services by the institutions we are talking about and by the individuals?

Dr. Cummings. That, of course, is a most important question. I suffer with that question, because here——

Mr. Flood. You don't want to overplay your hand here.

Dr. Cummings. You have to balance out the absolute requirement for information and not have charges that constrain people who have a right and a need to know.

On the other hand, we need some lever to reduce trivial or frivolous use.

Mr. FLOOD. You are obviously aware of this.

Dr. CUMMINGS. Painfully so.

PERSONNEL REDUCTIONS

Mr. FLOOD. Now you have a budget request increase of $367,000. It shows a decrease of seven jobs. Why is that?

Dr. CUMMINGS. The budget increases shown in the table before you are almost exclusively to bear the cost of mandatory pay raises. The only real increase in that budget is for the cost of literature.

Mr. FLOOD. There is a decrease of seven positions.

Dr. CUMMINGS. The decrease of seven positions is part of the overall NIH and I believe departmentwide need to cut back on positions. This was deemed to be our fair share.

LITERATURE ACQUISITION

Mr. FLOOD. You are asking for a total of $1,040,000 for equipment in 1976. Why do you need $1,040,000 for equipment in 1976 in view of the fact that you will be spending $940,000 for equipment in 1975? What is the gimmick there?

Dr. CUMMINGS. That term "equipment" is an unfortunate one for libraries. Under the category of equipment comes things like books and journals. Nearly all the money under equipment is for the acquisition of literature, books and journals. It is about $800,000.

Mr. FLOOD. I don't doubt that.

What does that have to do with my question? $1,040,000 in 1976 and you are spending $940,000 in 1975.

Dr. CUMMINGS. The cost of acquiring books and journals goes up at a rate of about 12 percent per year.

Mr. FLOOD. You include them under equipment.

Dr. CUMMINGS. Yes, sir. That is the strange nomenclature of the budget under which we must fit the acquisition of books and journals.

Mr. FLOOD. Mr. Michel.

Mr. MICHEL. On that question, why can't you make that visible in your budget, as books and journals for the library?

Dr. CUMMINGS. We do in our submissions to OMB. I think the language clearly shows that this is the purpose for which the money will be spent. In the budget books and journals do not appear as a line item. We would be happy to do so because you can appreciate it is a large part of our expenditure.

REGIONAL MEDICAL LIBRARIES

Mr. MICHEL. Where are these 10 regional medical libraries that you support and to what extent do you support them?

Dr. CUMMINGS. They are located in Boston, New York, Philadelphia, Chicago, Detroit, Omaha, Seattle, Dallas, Los Angeles, and in Bethesda. We provide in the aggregate support at a level of about $2.5 million for these 10 institutions to give their services regionally. Each then gets roughly about $250,000.

Mr. MICHEL. There seems to be a void in the Southeastern area geographically.

Dr. CUMMINGS. You are very perceptive. I neglected to mention Atlanta. There is a regional library in Atlanta.

Mr. MICHEL. Having named those cities, would those be in combination with medical complexes of those cities?

Dr. CUMMINGS. All of them are located in a medical institution of one nature or another. Seven of the 10 are in medical schools. Three of them are located in large, free-standing libraries.

GROWTH OF COMMUNICATIONS NETWORK

Mr. MICHEL. On this question of user charges, has the growth of the system come along faster than actual development of the system?

Dr. CUMMINGS. It is a foot race.

Mr. FLOOD. Will the gentleman yield?

Mr. MICHEL. Surely.

Mr. FLOOD. Along that line, what about the hardware? I happen to be a member of the Defense Appropriations Committee as well. I know something about telecommunication. You need a lot of hardware before you get into telecommunications. If you go from point A to point B, that is 200 miles, say. Where do the towers come from? Do you rent them from A.T. & T., or do you borrow them or does somebody give them to you, or what? Where do you get the equipment? That is quite a project.

Dr. CUMMINGS. This committee has been generous and has provided us with computer resources that we have in place.

Mr. FLOOD. That is just one thing.

Dr. CUMMINGS. We do not run our own lines or build our own towers. We use commercial telecommunication networks that exist domestically. We have a lease arrangement through which the more use we make the cheaper the unit cost.

Mr. FLOOD. When you talk about telecommunication from Alaska to Ohio, that is great, but knowing what I know about telecommunications since we started this business, and computers——

Dr. CUMMINGS. To complete my answer, I should point out as I did last year that NASA has been very generous to us and has allowed us to have access to the satellites that they have in place.

Mr. FLOOD. Without cost?

Dr. CUMMINGS. Without any cost to us.

We do pay for the ground terminals.

Mr. FLOOD. You are not in the satellite business yet?

Dr. CUMMINGS. No.

I don't think we are going to be building or launching satellites.

Mr. FLOOD. I don't mean building. They are up there.

Dr. CUMMINGS. We are using available time on those already in space.

Mr. MICHEL. What would you estimate would be your maximum output with the Medlars II system?

Dr. CUMMINGS. We expect to be able to deliver more than 600,000 searches in the next fiscal year. This will probably put us close to the point where there may be a deterioration in the time response. Our estimate is that we can go with our present configuration for about 2½ years before success is going to do us in.

SEARCHES

Mr. MICHEL. I notice a change in your original testimony from over 400,000 searches to 300,000. Why is that?

Dr. CUMMINGS. The number of Medline searches is 300,000 but the 400,000 figure includes Toxline and other searches.

My staff persuaded me this morning to deal only with Medline. We are giving more than 400,000 computer searches on all our data bases.

Mr. MICHEL. Do you have any figures on the average cost and time required for a search?

Dr. CUMMINGS. Yes.

The average thorough search of the literature can take place in less than 10 minutes. The average cost of searching is about $12 per hour.

One search costs about $2.40. Five would run about $12 per hour.

Mr. MICHEL. Are there any other computer systems of this nature established in any other countries that you know of?

Dr. CUMMINGS. I believe data bases such as ours are being worked in other countries.

I don't know of any as extensive as ours that has been generated de novo in other countries although Germany, Japan, and Sweden are very actively trying to get into this field.

Mr. MICHEL. We do not currently have any of those foreign countries abroad tying in, in any way, to our system, do we?

Dr. CUMMINGS. Yes; we do, sir. We receive from Sweden, West Germany, France, the United Kingdom, Canada, Australia, and Japan input into the system. It is in the form of indexing or abstracting which equates to $50,000 of effort from each of them for the privilege of their accessing our data base.

Putting that in an aggregate, we are getting in return about $400,000 in services and input into the service internationally to allow them to access the system.

FOREIGN LANGUAGE PUBLICATIONS

Mr. MICHEL. How is the information translated from one language to another?

Dr. CUMMINGS. Well, because half of the world's literature is in a foreign language, it does require members of my staff or our foreign partners to translate all of this literature into the English language. That does not mean that they translate it word for word, or line for line. They summarize it in the English language. Our system is an English language system which, I am pleased to say, all foreign partners are prepared to work with.

Mr. MICHEL. You feel it is your responsibility to get it translated into English; right?

Dr. CUMMINGS. We are not doing it for them. We are doing it for the American physicians who obviously cannot handle all the other languages.

Mr. FLOOD. To what extent is technical terminology used in all languages? Take a medical term, a word or even a phrase, especially if the derivation may be Latin. Whether it is or not, is that used interchangeably in your telecommunications?

Dr. CUMMINGS. We have developed standards in part working with the World Health Organization. But I would say largely over the course of the last century, we have developed a vocabulary and nomen-

clature of the medical literature that has become a standard so that a medical term like Parkinson's Disease means the same thing all over the world.

Mr. FLOOD. Do they say "Parkinson's Disease," or what?

Dr. CUMMINGS. By and large the vocabulary we have adopted for our use is now an international vocabulary. The problem is that physicians and scientists invent new terms as science progresses. We have to keep abreast of this and keep changing the dictionary and elaborate it.

Mr. FLOOD. I know that, but I am talking about what exists now primarily.

Dr. CUMMINGS. We try to have an international vocabulary and the World Health Organization also works in establishing these norms.

Mr. FLOOD. I would think so.

Thank you.

TOXLINE AND AVLINE

Mr. MICHEL. What has been the growth rate of the other systems such as Toxline and Avline?

Dr. CUMMINGS. I cannot give you precise data from memory. I can tell you the number of institutions that has signed up for these services has more than doubled in the past year.

I can provide you with precise data for the record if you would like it.

Mr. MICHEL. You might put in something.

Dr. CUMMINGS. It has grown exponentially.

[The information follows:]

The library performed aproximately 12,000 Toxline searches in fiscal year 1974. We estimate that the number will increase from 15,000 in fiscal year 1975 to aproximately 20,000 in 1976. The Avline system is currently in the test file stage and should be operational in fiscal year 1976.

COMMUNICATION NETWORK REQUIREMENTS

Mr. MICHEL. Do you anticipate that your present equipment will be able to keep up with demand?

Dr. CUMMINGS. Our estimates suggest that we will be able to keep up with demand for the next 2½ years, particularly by tuning the pricing structure. That is very important.

Mr. MICHEL. You use time frame and Medlars II. What does that suggest 2½ years from now?

Dr. CUMMINGS. It suggests, hopefully, that new technologies in the computer field will allow us to improve our configuration by having, say, discs that compress information more than it does now or that the processing will be speeded up. We are hoping that technology will make advances so our changes in configuration can keep up with the workload.

It also suggests, Mr. Michel, that we may have to decentralize our system more than we have. It may well be that Bethesda can no longer be the base from which we give these services. We may have to package it and put it in some other libraries.

Mr. MICHEL. Would it follow, then, that you would utilize those 10 or 12 regional centers we alluded to earlier? Is that the most natural?

Dr. CUMMINGS. Yes.

They now, of course, serve as regional search centers for the States in their community of interest, but they do not all have computer apparatus to actually run the tapes.

It is possible, I think, that in time they will. We may just have to package our material and have it operate in 8, 9, or 10 of the Centers.

We do have one backup operation in New York now. The State University of New York system maintains a backup operation to the NLM.

Mr. MICHEL. But to be practical, you could not very well have certain information at one regional Center and a concentration or a specialty in another, or is that practical?

Dr. CUMMINGS. I think if the integrity of the information is kept in big pieces, it is more practical and economical. If you fracture this information to little tiny units, it becomes cost-ineffective. That would be my estimate.

Mr. MICHEL. I was just thinking in terms of cost of leasing and lines, et cetera. If it were specialized and one specialty were on the east coast, then obviously all the information going to the west coast builds up a cost as distinguised from another discipline closer. It would average out, but your professional judgment would be one, offhand at least, that it would tend to hurt the system rather than enhance it.

Dr. CUMMINGS. I would be very glad to have some studies made of this important question and perhaps come prepared at a later date to give you the tradeoffs that we learned from this examination.

Mr. MICKEL. Since the chairman has made reference with respect to computers and how they originally came to us and in what size and description and then the first generation and second, et cetera, I am curious to know. I think in your own shop you had a MEDLARS–I, and MEDLARS–II. That was a growing technological improvement.

I am trying to look into the crystal ball for how many more dollars you will be asking us for 2½ years from now if both of us are still here.

Thank you, Mr. Chairman.

Mr. FLOOD. Is there any kind of understanding in the medical research scientific world that when you give birth to a new term that it should be based, the derivatives, on Latin and Greek, preferably?

Dr. CUMMINGS. Not anymore, I'm afraid.

Mr. FLOOD. That is too bad.

I was afraid of that.

Dr. CUMMINGS. At the turn of the century there was that kind of standard lexicography and taxonomy.

Now, you know, names are attached to people and geographic places. Eponyms are a terrible thing to contend with.

Mr. FLOOD. Mr. Patten.

Mr. PATTEN. The Doctor makes much of the audiovisual project up at Fairbanks. I wish some of you people would bring in some audiovisual. You have been talking here for an hour. I will bet you could put a couple of things on exihibit to prove your point a lot quicker. I dropped up to Dartmouth Medical College, which you did not mention this year in your presentation.

Dr. CUMMINGS. Yes, it is. That is one program which we are slowly withdrawing from to be picked up by the local community.

With regard to your comment on the use of audiovisuals, I know the committee would do better with those than with my New Jersey English.

Mr. PATTEN. No, I'm only kidding. I have heard some of these people say, "We learn 93 percent through the eye." I can understand your statement that the student up at Fairbanks, Alaska, is getting a great deal. That is very valid. We have a library at our medical school at Rutgers.

I only hear good words about it from our doctors. You do not help that school any?

Dr. CUMMINGS. Oh, yes, we have. Let me remind you first that the librarian who started that Rutgers medical library was recruited from our institution, a very fine gentleman.

Rutgers has received resource grant support along with many other new medical schools. We have a very close relationship with that medical school along with all others. They have benefited by the programs you support here.

Mr. PATTEN. It would be a pleasure to talk about this and 10 other things, but I will not, because we want to get to Dr. Schwartz. But if I had my way, I would put right in the middle of the medical school a building for family physicians. What are you doing for the fellow who is good enough to come out at 11 o'clock at night or 2 o'clock in the morning that I have in my neighborhood who is no specialist? Does he use your service?

Dr. CUMMINGS. Twenty-six percent of all the services we give now go to the family physician or the general practitioner. I can tell you, Mr. Patten, that that was not true 10 years ago. When I first came to the National Library of Medicine I was appalled to see how few physicians knew of its existence and knew of its resources available to them. That has climbed steadily. I am optimistic that the gentleman who is taking care of you at midnight is now learning that he can get rapid access to medical information to give you the latest treatment.

Mr. FLOOD. If you will yield, I am glad you mentioned that. I have been amazed—I have not admitted it—by the number of GPs that I meet in my own area who know about you and your operation in the last few years. I never heard it before but in the last 5, 7 or 8 years I have heard a lot about it.

Mr. PATTEN. As lawyers, our library is right at our side. My pride in the law office is my books.

Dr. CUMMINGS. Doctors should do the same.

Mr. PATTEN. The greatest doctor I ever knew was a general practitioner. What amazed me, he never stopped reading. He subscribed to the best journals. Every time I saw him he was reading or discussing, running into NYU or Columbia. Still you called him a general practitioner. You mentioned about continuing to learn in the field. It looks to me like you have the same kind of budget you had 10 years ago.

You are talking here about the growth and new cases. Back in 1974's budget you received $27,738,000. It seems to me, your budget stays about the same without taking into consideration inflation, sal-

ary increases and everything else. Of course, I will just tell you that this is my 41st budget. I started as mayor in 1934. At the local level they said, cut the budget 10 percent. We cut out recreation and the libraries. Nothing further, Mr. Chairman.

Mr. FLOOD. Mr. Smith.

MEDICAL LIBRARY ASSISTANCE

Mr. SMITH. Dr. Cummings, I note a reduction in funds available for library assistance grants from the level of 2 years ago. Will the reduced amount permit you to develop your biomedical communication plan in a manner adequate to meet the needs of our practicing physicians and other health workers? What effect will this cut in grant funds have on your regional medical library program and companion efforts to improve biomedical library resources?

Dr. CUMMINGS. The library assistance grant has been effective in increasing the capability of the medical libraries at the local level to respond to the needs of the practicing physician and allied health workers. The rate at which local medical library capabilities will be strengthened is dependent upon the funds available through the library assistance grant.

A lowered funding level reduces local effectiveness and results in increased demands upon the regional medical libraries (RML) by the local libraries. This increased burden on the RML seriously undermines its ability to be responsive to the burgeoning demand for medical information by the health community and adversely affects the total biomedical library network with more and more requests being referred across the country to the already overloaded National Library of Medicine.

Mr. SMITH. How do you assure yourself that the type of work being done with grant assistance is of a superior quality?

Dr. CUMMINGS. Our grants program benefits from the same peer review system that has proved so effective for other components of the NIH. Each application is assigned for scientific review to a study section composed of nonfederal consultants with subject expertise. The biomedical library review committee is comparable in function to the other study sections of NIH. For this committee, however, the subject expertise of its members spans a wide variety of disciplines including computer science, information science, librarianship and medical education. Grant applications for audiovisual programs are also routinely sent to the National Medical Audiovisual Center for technical review. Resource project grant applications are similarly sent to the appropriate regional medical library for comments as to their regional impact and implications. Peer review, as practiced at NIH, has an excellent track record; and I am assured therefore that work of superior quality is being identified and supported.

IMPROVEMENT OF HEALTH SCIENCE EDUCATION

Mr. SMITH. Dr. Cummings, how much attention are you giving to the need for improved educational activities in the fields of interest of the National Library of Medicine? For example, isn't there a need for close coordination of the educational portion of the responsibilities of

the NMAC, the Lister Hill Center, and the various activities supported by grants or contracts such as the regional medical libraries?

Dr. CUMMINGS. The support of improvement of health science education is one of the main objectives of the National Library of Medicine's Biomedical Communications Network. Its implementation is contributed to by all components of the Library. For example, the National Medical Audiovisual Center working with the Lister Hill Center and the Health Resources Administration has developed a program for the review, testing, abstracting, indexing and cataloging of multimedia educational materials of demonstrated value. The Lister Hill Center is actively pursuing various options for the development of economic effective distribution systems for this material as well as utilizing communication technology to facilitate learning.

The Lister Hill Center is particularly interested in the use of communications technology to minimize the effect of isolation of health scientists working in rural areas. Working with the National Medical Audiovisual Center and our regional medical libraries, programs are being developed with the Health Service Corps personnel to provide selected information in multiple formats. These needs for continual education of health practitioners constantly bring together not only all elements of the National Library of Medicine but also other Health agencies particularly HRA, HSA, and other NIH components.

All of these activities are coordinated in the Office of the Director, NLM.

MEDLINE

Mr. FLOOD. Mr. Conte.

Mr. CONTE. Dr. Cummings, you said that you were increasing your user charges in order to moderate the growth of the Medline system. How much are you increasing your user charges? How many searches do you expect to perform in 1976 with your increased user charges?

Dr. CUMMINGS. Effective February 1, 1975, Medline user charges were raised to $8 per connect hour to reflect a more recent analysis of communications costs, usage patterns, and to recover a greater portion of communications or accessing costs. Effective July 1, 1975, variable rates of $15 per connect hour during prime time hours (10 a.m. to 5 p.m. ET) and $8 per connect hour during nonprime time hours will be implemented. The National Library of Medicine will perform approximately 400,000 searches in fiscal year 1976.

MEDLARS

Mr. SMITH. Dr. Cummings, you said that more than 300 institutions are a part of your Medlars system. Do you expect this number to increase over the next year or several years? How does an institution join Medlars—is there a membership fee in addition to the user charge? How much does it cost to become part of the system?

Dr. CUMMINGS. Now that the NLM possesses greater computer capability, Medline services are being offered to a wide segment of the health community. On the average, 75 institutions join the Medlars system each year since its inception in 1972. The annual increase anticipated will be approximately the same next year.

An institution joins the Medlars system by application through one of the eleven regional medical libraries.

The applicant institution must acquire through purchase or lease, a terminal compatible with the network, and pay for installation costs. These are the principal costs associated with entry to the system. Once a center has become operational, monthly service charges are the only additional costs incurred.

REGIONAL MEDICAL LIBRARIES

Mr. CONTE. Dr. Cummings, where are your 10 regional medical libraries? How long, on the average, does it take from the placing of an order to the receipt of the book or journal needed through the interlibrary loan network?

Dr. CUMMINGS. The National Library of Medicine also functions as a regional medical library, therefore, a total of eleven "RML's" form the backbone of the biomedical library network. I will furnish a list for the record.

[The information follows:]

New England Region I, Francis A. Countway Library of Medicine, 10 Shattuck Street, Boston, Mass. 02115.
New York and Northern New Jersey Region II, New York Academy of Medicine Library, 2 East 103 Street, New York, N.Y. 10029.
Mid-Eastern Region III, Library of the College of Physicians, 19 South 22d Street, Philadelphia, Pa. 19103.
Mid-Atlantic Region IV, National Library of Medicine, 8600 Rockville Pike, Bethesda, Md. 20014.
East Central Region V, Wayne State University Medical Library, 4325 Brush Street, Detroit, Mich. 48201.
Southeastern Region VI, A. W. Calhoun Medical Library, Emory University, Atlanta, Ga. 30322.
Midwest Region VII, John Crerar Library, 35 West 33d Street, Chicago, Ill. 60616.
Midcontinental Region VIII, University of Nebraska, College of Medicine, 42d Street and Dewey Avenue, Omaha, Nebr. 68105.
South Central Region IX, University of Texas, Southwestern Medical School at Dallas, 5323 Harry Hines Boulevard, Dallas, Tex. 75235.
Pacific Northwest Region X, University of Washington, Health Sciences Library, Seattle, Wash. 98195.
Pacific Southwest Region XI, Center for the Health Sciences, University of California at Los Angeles, Los Angeles, Calif. 90024.

All regional medical libraries report interlibrary loan activities on a quarterly basis.

Throughout time measured is the length of time from receipt or request to the time the request is being sent out. About 85 percent of all requests are filled within the first 4 days of receipt.

USER CHARGES AND REIMBURSABLE INCOME

Mr. CONTE. Dr. Cummings, what is the total income of the National Library of Medicine, including user charges and reimbursable income from all sources?

Dr. CUMMINGS. The NLM will recover and expend, in addition to its annual appropriation, approximately $1.5 million for services it performs for other Government agencies in fiscal year 1975. In addition to its reimbursable activity, NLM operates under a user charge policy for its computerized search services. This policy permits NLM to apply its appropriated resources to building the data bases and to maintain the communications network while having the users pay the cost of accessing the system. It is anticipated that NLM users will be billed approximately $400,000 for these services in fiscal year 1975.

COPYRIGHT SUIT

Mr. CONTE. Dr. Cummings, I'm sure that we are all pleased that the Government has won its copyright suit. Has the Library submitted its own proposal for revisions in the copyright law to deal with its own problems in this area?

Dr. CUMMINGS. The NLM has not been asked to submit a legislative proposal to amend the copyright law. We have developed a position, however, concerningH.R. 2223, the proposed General Revision of the Copyright Law.

Our interlibrary loan practices, and those of the other libraries which constitute the regional medical library network, could possibly be regarded by some as an infringement of the revised copyright law as proposed in section 108(g)(2) of H.R. 2223. This section would prohibit the systematic reproduction and distribution of single copies of journal articles and of small parts of other copyrighted works. We would propose that subsection 108(g)(2) be either deleted or amended to permit a single copy of an article or brief excerpt from a book be made as "fair use." This modification, if incorporated in the final bill, would result in a copyright law which would make it possible for NLM and the other medical libraries in this country to continue to effectively serve the health science community by sharing their resources.

LISTER HILL CENTER BUILDING

Mr. CONTE. As you may recall last year you had a little discussion with the chairman about plans for the construction of the Lister Hill Center. Could you give me a progress report on the Center's construction and plans?

Dr. CUMMINGS. We have made considerable progress since the time of our hearings last year. The final architectural and engineering drawings are now complete. As soon as funding becomes available we can begin the construction of this facility. This Center, when completed, will enhance the NLM's ability to fulfill its congressional mandate to develop a comprehensive, integrated biomedical communications network and at the same time will relieve a serious space problem that exists in our present facility.

COLLABORATION WITH THE BUREAU OF HEALTH RESOURCES DEVELOPMENT

Mr. CONTE. Dr. Cummings, could you give me some more examples of your cooperative work with the Bureau of Health Resources Development in producing teaching materials for the health community?

Dr. CUMMINGS. The collaborative program between the Bureau of Health Resources Development and the National Library of Medicine's National Medical Audiovisual Center has produced teaching materials now in use in medicine, dentistry, nursing, and allied health professions. Instructional materials are produced by BHRD/NLM as part of research and development efforts to discover effective ways for the health professional community to utilize instructional technology in teaching. The results of these project activities are used in training and advisory service programs, and are used to encourage support and production of instructional media by health professional

schools and other professional groups. The NLM currently has 71 ongoing cooperative projects with BHRD. Noteworthy examples are efforts in opthalmology on opthalmoscopy, congenital heart disease, and hypoglycemia of the newborn.

COLLABORATION WITH THE NATIONAL HEALTH SERVICE CORPS

Mr. CONTE. I am very interested in the work of the National Health Service Corps, for which we are considering the authorization later this week, and I wonder if you could tell me some more about your program with the Health Services Administration for Health Service Corps medical education?

Dr. CUMMINGS. The National Library of Medicine and the Lister Hill National Center for Biomedical Communications are working with the Health Services Administration in developing improved information and communication networks for the doctors and dentists in the National Health Service Corps. We want to decrease the sense of professional isolation experienced by members of the Corps. Our immediate purposes are to increase the opportunities for continuing postgraduate education and to facilitate the consultative services which are required for high quality patient care. The approach is to develop better communication networks with major patient referral centers and with regional medical libraries. In addition, various kinds of audiovisual and computer instructional packages are being identified and made available for use by the health professionals in their office. A longer range objective for the Lister Hill Center is to define its proper role in supporting educational efforts designed for practicing health professionals. We continually ask ourselves, what is needed and how should the information be supplied? The collaboration with the National Health Service Corps gives us the opportunity to work with a vigorous group of relatively young practitioners who can test the effectiveness of various approaches proposed.

TOXLINE

Mr. CONTE. Dr. Cummings, how much does it cost to get hooked up to your Toxline system? Is this the kind of thing that would be useful for local toxicology and poison control centers to subscribe to, or is this basically a research resource?

Dr. CUMMINGS. All charges associated with entry into the Toxline system are built into the current user rate of $15 per connect hour. Toxline covers such a broad area of information that it is considered a valuable data resource to local toxicology and poison control centers serving the health communities throughout the country.

BIOMEDICAL COMMUNICATION RESEARCH AND DEMONSTRATION PROJECTS

Could you provide a summary of some of the demonstration projects which were funded through the Lister Hill Center during the past year?

Dr. CUMMINGS. I would be glad to submit a summary for the record.

[The information follows:]

During the past year the Lister Hill National Center for Biomedical Communications has supported the following demonstration projects:

Experimental computer-assisted instruction.—This project is designed to foster the interinstitutional sharing of computer-based instructional resources among medical schools, hospitals, and other health-related organizations. More than 60 institutions have participated.

Application technology satellite–6 (ATS–6).—This project represents an effort to implement a coordinated telemedicine and health information system in Alaska and an experiment supporting decentralized medical education with the University of Washington and the States of Washington, Alaska, Montana, and Idaho.

New Hampshire/Vermont Medical Interactive TV Network.—This project provides a two-way interactive television system to be used in rural communities for delivering postgraduate educational programs for health practitioners. In addition, the feasibility of medical consultations being conducted over long distances has been explored.

Cable television for consumer health education.—This project is designed to explore the application of closed-circuit television to the dissemination of health information to an innercity geriatric population.

Mr. CONTE. How do you make sure that your projects will become self-supporting if they are successful? Suppose they aren't successful—what happens to them? Have you had any failures you could tell us about during the past year?

Dr. CUMMINGS. The Lister Hill Center program has been deeply concerned about the problems of converting successful demonstration projects into operational systems. We are particularly cognizant of the fact that coordinative and effective planning is necessary early in the experimental project in order to insure a smooth transition into an operational mode. The Center strives to obtain local self-sufficiency whenever possible and turns to other agency support as an alternative when necessary. The Lister Hill program itself does not have the funding or the mandate to support actual operating systems.

If an experimental project were judged unsuccessful for any reason we would, of course, terminate our support. We are pleased to report that our experiments over the years have been most useful in fostering better health care and health education. Success, as measured in terms of actually implementing systems after their demonstration period has ended, remains an unanswered question. A number of our projects are currently in this transition stage. The New England Interactive Television Network is a case in point. The purpose of this experiment was to evaluate the effectiveness of interactive television in bringing continuing education and improved health care to rural settings. Its effectiveness has had demonstrated and we are now engaged in efforts to place the network on a self-sustaining basis. A management consulting firm has been retained to examine the management practices and operational funding required for the project to become self-supporting.

COMMUNICATION TECHNOLOGY SATELLITE PROJECT

Mr. CONTE. Could you tell me some of the uses for the satellite you plan to launch in December? What are some of the things being planned by the various health agencies? Could a satellite system of this sort be used for international biomedical communication? Are any plans underway for such an endeavor?

Dr. CUMMINGS. The communications technology satellite, CTS, which is scheduled to be launched in December 1975, will include the coordination of program and evaluation planning and the provision of technical engineering support in six areas of application,

namely, postgraduate education for practicing health professionals, dissemination of medical research results, specialized educational programs for targeted health problems, teleconferencing, decentralized medical education, and health delivery experiments.

We are involved in planning activities with various organizations within the health agencies. Within the National Institutes of Health, the Heart and Lung Institute plans to sponsor educational programs in the control of hypertension. The Cancer Institute plans to involve their comprehensive centers in Denver and Seattle in a series of "Grand Round Conferences" which are designed to provide current information on cancer diagnosis, treatment, and control to practicing physicians. Within the Health Resources Administration, the Division of Dentistry is planning experiments designed to provide dentists and dental auxiliaries access to computerized private practice simulation models. The models will be developed with the goal of improving health delivery practices.

The Bureau of Health Resources Development is examining programs responsive to the needs of the practicing primary care physican. The Food and Drug Administration has indicated interest in exploring the potential of CTS communications for improving the dissemination of information on medical devices and new drugs.

With respect to the use of satellite systems for international biomedical communications, the Lister Hill Center at present is not planning such effort, although this clearly is technically feasible.

NEW ENGLAND INTERACTIVE TELEVISION NETWORK

Mr. CONTE. What have you learned from your funding of the New England Interactive Television Network that can be applied to future such systems? Do you think that the New England system can become self-sustaining? How?

Dr. CUMMINGS. A management consultant firm was engaged by the Lister Hill Center to study the management and financial needs incident to the New Hampshire/Vermont Medical Interactive TV Network becoming a self-supporting operation. From the evidence at hand, we believe that future networks will need to be justified on their potential operational value. If the tangible cost benefits of a proposed TV network cannot be predicted at the start, then the benefits will probably never be realized. Interactive television projects have high initial costs, require the early formulation of the long-run objectives, and must have specific operational goals.

We think that the New England network can become self-sustaining if properly managed. There is no question that it provides beneficial services. The problem is to adjust the cost of the services to users' ability to pay.

Mr. CONTE. I have no further questions.

Mr. FLOOD. Thank you, Doctor.

Dr. CUMMINGS. Thank you, sir.

Justification of the Budget Estimates

Appropriation Estimate

NATIONAL LIBRARY OF MEDICINE

To carry out, to the extent not otherwise provided for, Section 301 with respect to health information communications and Parts I and J of Title III of the Public Health Service Act, [$28,450,000] *$28,815,000.*

For the National Library of Medicine for the period July 1, 1976, through September 30, 1976, $6,572,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation 1/

	1975 Estimate 2/	1976
Appropriation	$28,450,000	$28,815,000
Comparative transfer to:		
"Office of the Director" (Transfer of Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	-2,000	---
Total Obligations	$28,448,000	$28,815,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 - $1,500,000; 1976 - $2,000,000

2/ Excludes 1973 restoration in the amount of $182,000

Summary of Changes

1975 Estimated obligations	28,448,000
1976 Estimated obligations	28,815,000
Net Change	+367,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-In:				
1. Annualization of 1975 Pay Cost Increases	---	---	---	+125,000
2. Within-Grade Pay Increases	---	---	---	+165,000
3. FTS Rate Increase	---	---	---	+ 21,000
4. Literature Acquisition	---	---	---	+100,000
5. Increased Cost of Services and Supplies	---	---	---	+ 15,000
Subtotal Increases	---	---	---	+426,000
B. Program:				
1. MLAA - New Grants	---	$4,743,000	---	+334,000
Total, increases	---	---	---	760,000
Decreases:				
A. Built-In:				
1. Payment to National Institutes of Health Management Fund	---	---	---	-59,000
B. Program:				
1. MLAA - Non-Competing Continuation Grants	---	4,743,000	---	-334,000
2. Lister Hill Nat'l Center for Biomedical Communications	26	---	-3	---
3. Nat'l Medical Audiovisual Ctr.	102	---	-2	---
4. Library Operations	252	---	-2	---
Total, decreases	---	---	-7	-393,000
Total net change		---	-7	+367,000

Explanation of Changes

Increases:

A. Built-In:

1. These increases will provide $125,000 for annualization of 1975 pay cost increases ($6,000 for the Lister Hill National Center for Biomedical Communications, $22,000 for the National Medical Audiovisual Center, $5,000 for the Office of Computer and Communications Systems, $30,000 for Library Operations, $6,000 for the Toxicology Information Program, and $56,000 for Research Management and Program Services);

2. $165,000 for within-grade pay increases ($10,000 for LHNCBC, $35,000 for NMAC, $85,000 for LO, $10,000 for TIP, and $25,000 for RM&PS);

3. $21,000 (RM&PS) for increased cost in 1976 for using the Federal Telecommunications System;

4. $100,000 (LO) for literature acquisition;

5. $15,000 (RM&PS) for increased costs of services and supplies;

B. Program:

1. $334,000 (MLAA) for eleven new grants for training specialists to integrate computer technology into all phases of clinical medicine.

Decreases:

A. Built-In:

1. A decrease of $59,000 in the assessment to the NIH Management Fund for centrally furnished services.

B. Program:

1. A decrease of $334,000 for eight grants in the area of Medical Library Resources.

Obligations by Activity

Page Ref.		1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
307	Medical Library Assistance						
	Total.....	---	6,333,000	---	6,333,000	---	---
	Direct Operations:						
309	Lister Hill Nat'l Ctr. for Biomedical Communications:						
	(a) Project contracts.	---	2,025,000	---	2,025,000	---	---
	(b) Other direct.....	26	669,000	23	685,000	-3	+ 16,000
312	Nat'l Medical A/V Ctr:						
	(a) Project contracts.	---	325,000	---	325,000	---	---
	(b) Other direct.....	102	2,599,000	100	2,656,000	-2	+ 57,000
313	Library Operations:						
	(a) Project contracts.	---	1,920,000	---	1,920,000	---	---
	(b) Other direct.....	252	8,094,000	250	8,314,000	-2	+220,000
315	Toxicology Information:						
	(a) Project contracts.	---	940,000	---	940,000	---	---
	(b) Other direct.....	16	890,000	16	906,000	---	+ 16,000
317	Research Management & Program Services:						
	(a) Project contracts.	---	---	---	---	---	---
	(b) Other direct.....	79	4,653,000	79	4,711,000	---	+ 58,000
	Subtotal.....	475	22,115,000	468	22,482,000	-7	+367,000
	Total Obligations...	475	28,448,000	468	28,815,000	-7	+367,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions.....	475	468	-7
Full-time equivalent of all other positions.....	40	40	---
Average number of all employees.....	534	527	-7
Personnel compensation:			
Permanent positions.....	8,246,000	8,506,000	+260,000
Positions other than permanent.....	529,000	529,000	---
Other personnel compensation.....	117,000	117,000	---
Subtotal, personnel compensation.....	8,892,000	9,152,000	+260,000
Personnel benefits.....	814,000	844,000	+ 30,000
Travel and transportation of persons.....	160,000	160,000	---
Transportation of things.....	24,000	24,000	---
Rent, communications and utilities.....	2,307,000	2,307,000	---
Printing and reproduction.....	369,000	369,000	---
Other services:			
Project contracts.....	5,210,000	5,210,000	---
Payment to NIH Management Fund.....	1,755,000	1,696,000	- 59,000
Other.....	1,346,000	1,382,000	+ 36,000
Supplies and Materials.....	298,000	298,000	---
Equipment.....	940,000	1,040,000	+100,000
Grants, subsidies and contributions.....	6,333,000	6,333,000	---
Total obligations by object.....	28,448,000	28,815,000	+367,000

Authorizing Legislation

Legislation	1976 Authorized	1976 Appropriation Requested
Public Health Service Act		
Section 381 - Purpose and Establishment of Library	Indefinite	$22,482,000 2/
Health Services Research, Health Statistics, and Medical Libraries Act of 1974		
Section 394 through 398	$20,000,000	6,333,000 2/
Total		$28,815,000

2/ Funding estimate only

National Library of Medicine

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	9,185,000	9,184,000	9,684,000	9,684,000
1967	19,231,000	20,154,000	20,254,000	20,254,000
1968	21,162,000	18,662,000	21,162,000	19,912,000
1969	19,172,000	16,997,000	19,020,000	18,008,500
1970	22,882,000	19,682,000	19,682,000	19,682,000
1971	19,769,000	19,843,000	22,307,000	20,843,000
1972	21,981,000	22,781,000	25,086,000	24,086,000
1973	24,994,000	28,488,000	28,988,000	28,488,000*
1974	24,994,000	25,796,000	25,796,000	25,426,000**
1975	27,738,000	28,048,000	29,348,000	28,448,000
1976	28,815,000			

*Note: This appropriation authority was the continuing resolution. The appropriations amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

**Appropriation after reduction.

National Library of Medicine

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	9,185,000	9,185,000	9,685,000	9,685,000
1967	19,231,000	20,092,000	20,192,000	20,192,000
1968	21,162,000	18,662,000	21,162,000	19,912,000
1969	19,172,000	17,149,000	19,172,000	18,160,500
1970	22,882,000	19,682,000	19,682,000	19,682,000
1971	19,769,000	19,769,000 ,	22,233,000	21,440,000
1972	21,981,000	22,781,000	25,086,000	24,127,000
1973	28,568,000	28,568,000	29,068,000	28,568,000 1/
1974	24,994,000	25,871,000	25,871,000	25,871,000 2/
1975	27,738,000	21,768,000 3/	29,350,000	28,450,000
1976	28,815,000			

1/ This appropriation authority was the continuing resolution. The appropriations amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

2/ Appropriation after reduction.

3/ Excludes Medical Library Assistance Grants not considered by House due to lack of legislative authorization.

Justification

National Library of Medicine

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	475	9,706,000	468	9,996,000	-7	+290,000
Other expenses.....	---	18,742,000	---	18,819,000	---	+ 77,000
Total.....	475	28,448,000	468	28,815,000	-7	+367,000

General Statement

The National Library of Medicine operates as the nation's principal national medical information resource by acquiring, organizing and distributing health related information in all forms. In order to adequately share this valuable health science information, NLM has developed a National Biomedical Communications Network to link major health care facilities, medical education centers and research institutions. It also has the specific responsibility to strengthen the nation's medical libraries and information services through resource, research, training and publication support.

The NLM collects materials exhaustively in 40 broad biomedical areas and, to a lesser degree, in related subjects such as general chemistry, zoology, botany, and psychology. The Library continues to expand its on-line bibliographic retrieval system MEDLINE (MEDLARS on-line) to more fully serve the health community. This national and international telecommunication-based science information network now serves about 250 institutions throughout the United States and at points abroad. Additionally, CANCERLINE, an on-line data base of cancer related citations and abstracts provided by the National Cancer Institute, has been added to facilitate worldwide cancer research.

The first half of FY 1975 saw the completion and acceptance of NLM's second generation computerized information system, MEDLARS II. This system is a greatly improved successor to the pioneering MEDLARS I, which had been in operation since 1963. With a much enhanced vocabulary capability, MEDLARS II will provide more efficient, specific, and rapid bibliographic information retrieval. It also will permit the entry of author abstracts of journal literature into the MEDLINE data base. Plans have been developed to increase the user charges from $8 to $15 per connect hour. This is being done to moderate growth of the system. Any excess proceeds will be returned to the U. S. Treasury.

NLM's Lister Hill National Center for Biomedical Communications was established in 1968 with a mandate to develop networks and information systems to improve health education, medical research, and the delivery of health services. An additional role assigned was to serve as the focal point within DHEW for the development and coordination of biomedical communications networks. In attempting to perform these functions, the Center has been confronted with the question of how to produce the most benefit from its limited resources. This has not been an easy question to answer. The need for improved biomedical communications is great, and the Center is acutely

aware that many aspects of biomedicine could benefit from the application of advanced communications technology and programming. Constrained by limited levels of funding and manpower, however, the Center has been forced to choose projects carefully. Broadly speaking it will concentrate its major efforts in the area of communications for health professional education, with an emphasis on improving clinical proficiency and therefore the quality of health care. Also because of limited resources, the Center will continue to stress exploration and demonstration rather than sustained operational support. An educational mission lends itself far more naturally to such an emphasis than does any direct intervention in health care delivery or basic biomedical research. An added benefit of concentration in this area is that a small investment can have a proportionately greater impact. By "education" we do not mean merely the relatively brief span of time which a health practitioner spends obtaining his or her professional credential. The maintenance of proficiency in the health professions requires a lifetime of learning, and the Center will devote particular attention to the communications support for continuing education of practicing health professionals.

In February 1975, the Lister Hill Center took a further step towards fulfilling its role as coordinator of a national biomedical communications network. In anticipation of a satellite to be launched jointly by the American and Canadian governments in December 1975, the Center hosted a meeting of representatives from all of DHEW's health agencies. The purpose was to inform them of the impressive capabilities of the new satellite and to stimulate planning in the health agencies for suitable programming. The satellite will provide nationwide coverage and require relatively small ground terminals, thus offering a high degree of flexibility for two-way audiovisual programs between broadcasts.

The National Medical Audiovisual Center (NMAC), located in Atlanta, Georgia, administers programs to improve the quality and facilitate the use of biomedical audiovisuals in support of health care and education. In its efforts to enhance educational efficiency and innovation in schools of the health professions, NMAC seeks the advice of major national health professional organizations to ensure that its programs focus on the areas of greatest relevance to the biomedical community.

Through its programs of medical library assistance, NLM provides grants for training, research, special scientific projects, publications, and medical library resources, and contracts for a national network of Regional Medical Libraries.

Emphasis in the training program is on producing specialists who can integrate computer technology into all phases of clinical medicine--teaching, practice, and research. Research grants are intended to help medical libraries find more efficient means of meeting the biomedical information needs of the clinical, research, and academic communities which they serve. Resource grants support the establishment, expansion, and improvement of the basic collections and services of medical libraries. With this assistance, for example, libraries can acquire a core collection of monographs and journals most frequently needed by local health practitioners. This permits the small local library to meet the bulk of its users' information needs without the delays involved in borrowing from a more distant facility. In those few instances where the local library does not have the material requested, it can call on the nearest Regional Medical Library (RML). By helping to support a network of such RML's covering the entire nation, NLM guarantees smaller community medical libraries access to health science literature on the same basis as the larger libraries. Services provided by the RML's include document delivery and reference assistance.

All of NLM's programs are based on the premise that effective communication and exchange of information among the world's scientists and health care

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practitioners will lead to better research and patient care with minimal duplication of effort. More importantly, improved information transfer will narrow the gap between the generation of new knowledge in the laboratory and the application of that knowledge to the treatment and prevention of illness.

The FY 1976 budget request will permit the National Library of Medicine to continue at approximately the same level of program activity as in the previous year. The areas in which there would be a shifting of emphasis and, in some cases, a modest expansion of on-going activity, are detailed below.

Medical Library Assistance Programs

Authorizing Legislation: Health Services Research, Health Statistics, and Medical Libraries Act of 1974

	1975 Estimate		1976 Estimate		Increase or Decrease	
	No. of Awards	Amount	No. of Awards	Amount	No. of Awards	Amount
Non-competing Continuation Grants..	63	4,743,000	55	4,409,000	- 8	-334,000
New Grants.....	59	1,590,000	70	1,924,000	+11	+334,000
Total.....	122	6,333,000	125	6,333,000	+ 3	---

NLM's programs of Medical Library Assistance are designed to meet the national need for more effective health information services. They provide grants to train professional personnel, improve resources and services of libraries, produce medical reviews and conduct research for improved application of information and communication technology. In addition, contracts assist in the development of a network of Regional Medical Libraries with the necessary resources and services to provide backup support locally for other medical libraries throughout the United States.

Training grants have supported the education of medical librarians, biomedical communications specialists, and other professional personnel essential to the health sciences information system. Over the past eight years the grants have supported the training of approximately 650 such individuals, most of whom now occupy positions of leadership throughout the country. By 1974 the critical shortage of medical librarians had been eliminated and program emphasis was shifted to the training of specialists who can effectively integrate computer technology into all phases of clinical medicine--teaching, practice, and research. Of the 11 grants funded in FY 1975, which supported the training of 55 individuals, all but two were in this area of interface between computers and medicine. In FY 1976 the emphasis will continue to be on training to involve health scientists in the medical applications of computers.

Research grants support projects in medical library science, information science, biomedical communications, and educational technology. In FY 1975, for example, a team of physicians and information specialists was supported in the investigation of computer-aided decision making. Another research team studied the information needs of practicing physicians, particularly as related to their continuing education requirements. Approximately 30 more Research grants will be funded in FY 1976. Potential projects include studies

of the impact of new information systems on health practitioners; the development of new information handling systems; and an analysis of educational technology and curriculum design as applied to the health sciences.

Special Scientific Project grants support distinguished health scientists in the full-time analysis of major findings in their respective fields. Their results are published in monographs that facilitate the accessibility of their findings. Four awards were made in 1974 and three will be made in 1975. One review will cover the biologic and therapeutic aspects of one of the very few types of cancer for which chemotherapy has proven successful. The work suggests new theoretical insights which may be applicable to other types of malignancies. Another will provide a comprehensive, critical review of all literature concerned with hepatitis, a major cause of disability and death.

Medical Library Resource grants are designed to assist in the improvement of the nation's health science libraries. These awards are not given to provide operating subsidies to libraries or to supplant existing support but are in fact intended to encourage increased financial support for the libraries by the institutions that they serve and the communities in which they are located. One-year, non-renewable improvement grants for up to $3,000 are made to health institutions--usually hospitals--which can demonstrate a need to establish basic collections and services. The FY 1976 budget estimate will support the award of 15 such grants.

In addition to the one-year improvement grants, NLM awards a second type of Medical Library Resource grant. These project grants are funded for up to three years with a ceiling of $200,000 for any budget period. They are intended to make the growing scientific literature more readily accessible to health professionals throughout the nation and to introduce or demonstrate new information science technology. In FY 1976 NLM will fund an estimated 45 grants of this type.

In FY 1975 Medical Library Resource grants have supported cooperative programs in which a strong library undertakes to provide training, consultation, and loan services for small community hospitals and clinics; studies on speeding the delivery of information through modern communications devices and automation techniques; and projects which, after an assessment of the actual information needs of health professionals, strengthen the information resources of an institution accordingly. In FY 1976 the grants will continue to complement NLM's Regional Medical Library program by upgrading the resources of local libraries within each region. In particular, NLM will support formal agreements among local hospitals to promote greater cooperation.

The Library's Publication Grant Program provides support for non-profit studies in the biomedical sciences. One recent publication was the first of a series of collaborative reviews of allied health education and research, prepared by outstanding authorities in health care disciplines. Modern developments in medicine have created a need for new allied health specialists trained in increasingly complex technologies. This new series of collaborative reviews constitutes a timely appraisal of the situation and evaluates innovative programs for meeting the serious need for specialized health personnel.

NLM contracts provide support for a national network of ten Regional Medical Libraries (RML's). The RML's, selected because of the depth and scope of their resources, provide an array of services which have clearly demonstrated that cooperative networking among health institutions of all types and sizes is not only feasible but economically imperative. The foundation of the developing network is the successful interlibrary loan program. Over 92 percent of the interlibrary loans made by the RML network are provided within four days of the receipt of the request. Reference, bibliographic, educational, and consultative services are also important activities of the RML's. The National

Library of Medicine provides back-up service for the RML's and also serves as the RML for the Mid-Atlantic Region. By making available to the RML network its advanced on-line systems such as MEDLINE, SERLINE, and CATLINE, NLM considerably broadens the availability of bibliographic information in all parts of the country.

The number of interlibrary loans supported by the RML's in FY 1975 remained at approximately the FY 1974 level of 500,000. The leveling off is indicative of strengthened resources at smaller, local libraries and increased sharing among them, which are important objectives of NLM's Medical Library Assistance programs. Utilization of and participation in the network by the health community is expected to increase substantially in FY 1976 for four major reasons: (1) health professionals have become increasingly aware of the utility and availability of interlibrary loans; (2) the continued development of MEDLINE will afford direct and greatly improved access by RML clients to a data base which is most relevant to a health professional's requirements; (3) many of the proposed national health care and health education systems, such as Health Maintenance Organizations, Area Health Education Centers, and Professional Standards Review Organizations, will place additional information requirements on health professionals; (4) the prohibitively high cost of purchasing biomedical literature will force smaller libraries to form local consortia which will satisfy a significant portion of the health information demands placed on them. While it is not anticipated that the federally subsidized interlibrary loans will increase in FY 1976, the main thrust of the program will be directed at refining the network at the local levels so that information needs can be met without sacrificing quality of service.

Lister Hill National Center for Biomedical Communications

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	26	541,000	23	557,000	-3	+16,000
Other expenses.....	--	2,153,000	--	2,153,000	--	---
Total.....	26	2,694,000	23	2,710,000	-3	+16,000

The Lister Hill Center encourages the application of advanced computer and communication technologies to the solution of biomedical information problems. Microwave, cable television, data communications, computer-assisted instruction and satellite relay networks are among the experimental and operational technologies applied by the Center.

1. Satellite Communications: For the last several years the Center has supported an experimental satellite communications network in Alaska, where sparse settlement, rugged terrain, and severe climate make conventional communications difficult or impossible. The network, which utilizes a NASA Applications Technology Satellite (ATS-1), links remote native villages with Indian Health Service hospitals and medical centers in Alaska. A careful evaluation has shown a fourfold increase in the number of patients being treated with a doctor's advice since the network began. On the basis of that success, the Center has provided the Indian Health Service with projections for other telecommunications projects aimed at improving health care delivery and medical education.

In FY 1975 the Center expanded the ATS-1 remote medical consultation network to support a series of experiments made possible by the recently launched ATS-6 satellite, which has greater capabilities than its predecessor. The ATS-1 communications link was broadened to connect native village clinics, medical centers, and the Tanana, Alaska Hospital with the Indian Health Service information service in Arizona. Through this link-up the village clinics are able to obtain up-to-date medical records on all listed village residents, thereby greatly assisting the health professional in patient care. In addition, five of the ATS-1 voice terminals have been made into operational audio links for the ATS-6 experiments, which already have proven to be a major improvement to the Alaskan biomedical communications network.

With the advent of the ATS-6 satellite, the communications network has acquired the capability for two-way live television transmission. Under the Center's direction, seven satellite telecommunications terminals have been installed and operated in the states of Alaska and Washington to support the ATS-6. Some of the studies are evaluating the effectiveness of live television consultation between physicians at Indian Health Service hospitals and small, remote clinics manned by health aides and other "physician-extender" personnel. Others are studying the use of interactive television communications in support of medical education. For example, interactive video, audio and physiological data transmissions have been used to link basic science students at the University of Alaska with students and faculty at the University of Washington Medical School. A similar linkup has connected the school with medical students receiving clinical training under physicians some distance away at Omak, Washington. The transmissions have included lectures and demonstrations, administrative and educational conferences, computer-assisted evaluation, medical consultation, grand rounds, and other continuing medical education programming.

In FY 1976 the Center will continue its experimental use of satellite communications to promote more effective dissemination of medical information among students, practitioners, and research scientists. The ATS-6 medical education program will be extended to other institutions to support the decentralized medical school project and provide continuing education for physicians, residents, and allied health care personnel at remote sites.

2. New England Interactive Television Network: From June 1970 to October 1973, the Center supported a medical interactive TV network in New Hampshire and Vermont. The purpose was to evaluate the effectiveness of interactive TV for bringing formal classroom instruction, continuing education, and improved health care to rural settings. Now that its effectiveness has been demonstrated, the Center has been working to place the network on a self-sustaining basis. A management consulting firm has been retained to determine whether the individual and institutional users of the network value its services sufficiently to support them financially.

In FY 1975 the network has continued to provide 40 hours of interactive programming per week to between 1,000 and 2,000 viewers at seven institutions. Emphasis during this period has been on beginning the transition to a fully self-sustaining operation, which has involved negotiations with the Federal Communications Commission, seven user institutions, and the primary contractor, Dartmouth Medical College.

Although FY 1976 will be the last year of NLM funding for the network, information produced by the project will be invaluable in planning broadband biomedical communication networks in the future.

3. Computer-Assisted Instruction (CAI): In FY 1972 the Lister Hill Center initiated an experimental computer-assisted instruction (CAI) network. The network has connected computer data bases at Ohio State University, Massachusetts General Hospital and the University of Illinois Medical Center, with 80 other

institutions, primarily medical schools. Programs offered over the network have been used for undergraduate, graduate, and continuing medical education for a variety of purposes: as an introduction to CAI, a complement to local CAI activities, a resource for experimentation in education, and a tool for remedial instruction.

Users of the network have always had to provide their own computer terminals, communications costs to the nearest access point in the network, and salaries of participating faculty members. In February 1974, users began sharing communications costs more broadly, paying $5.00 per connect hour. The implementation of user charges has produced only transitory decreases in both the number of institutions and the hours of usage.

The experiment in network distribution of particular computer-assisted instructional materials is scheduled to terminate in May 1975. Forty-five of the user institutions have formed the Health Education Network Users Group. This organization is working with the Lister Hill Center and the network contractors to make a transition to a network managed and financed by the users. At the same time, the Center is planning a broader involvement with the many problems inherent in using computer-assisted instruction in medical education. This will include translation and standardization of CAI formats, and evaluation both of the content of computer-assisted programs and of their educational effectiveness.

4. Continuing Education of Health Professionals: Continuing education is now recognized as an important means of conserving health manpower, upgrading the quality of medical care, and promoting the flow of new information to the health care community. There is general awareness that continuing education and the benefits derived from it occur most readily in the university setting. The problem is that the majority of health care professionals and the populations they serve are not located near academic health centers. There are however, latent educational resources available in local community hospitals. The Lister Hill Center has postulated that continuing education can be improved by structuring programs among groups of hospitals to mobilize this latent resource.

The Lister Center is encouraging the development of such hospital educational consortia, and is interested in developing appropriate communications systems for their most efficient operation. As a first step the Center has completed a study of several of the more effective consortia in current operation. It now plans to test selected communications systems and computer-assisted instruction programs in the community hospital environment. Goals will include: determining the critical mass of a functioning system and optimal mix of local, regional or national networks; selecting and testing appropriate communications modalities; and studying the administrative structure necessary for effective operation.

The Center also will be participating with the Health Services Administration (HSA) in the creation of a Continuing Medical Education Program for the medical officers of the National Health Service Corps. The Center will support the development of an interactive communication system to make possible (1) the acquisition of new information and technical skills in family medicine, internal medicine, pediatrics, obstetrics and the treatment of trauma; (2) the periodic reassessment of cognitive knowledge; (3) consultative services for specific problems in the day to day practice of medicine; and (4) the development of a process for auditing the quality of patient care appropriate to both the ambulatory and the hospital setting. Another objective is to reduce the degree of professional isolation experienced by these physicians by developing rewarding patterns of self-learning, consultation, and evaluation. A third objective is to experiment with new methods of assessing the quality of professional services.

National Medical Audiovisual Center

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	102	1,956,000	100	2,013,000	-2	+57,000
Other expenses.....	---	968,000	---	968,000	---	---
Total.....	102	2,924,000	100	2,981,000	-2	+57,000

The National Medical Audiovisual Center (NMAC), located in Atlanta, Georgia, applies audiovisual technology to the special needs of biomedical scientists, practitioners, and educators. The Center's primary focus is to stimulate the development and use of effective audiovisual media in schools of the health professions and in the continuing education of health professionals.

In FY 1975 NMAC worked closely with schools of the health professions and national professional organizations, such as the Association of American Medical Colleges (AAMC), to identify and develop applicable models of instructional media. By seeking the advice of informed professionals at the earliest stages of development, NMAC hopes to assure that the resulting products will be appropriate and actually utilized by the health professional community. Significant projects already have been carried out in anatomy, dentistry, and other disciplines.

During FY 1975 NMAC responded to 3,000 inquiries for instructional media information and provided 65,000 film loans and 2,000 videotape duplicates of instructional programs. Technical assistance in the development or use of audiovisual media, equipment, and communications systems included 3,000 technical reports and instructional monographs; 280 site consultations and in-house working sessions; and 15 audiovisual technology workshops. The Center continued to develop its on-line bibliographic information retrieval system, AVLINE (Audiovisuals on-line), for operation on NLM's computer to be made available on NLM's nationwide on-line retrieval network. AVLINE will contain records of audiovisuals which have been evaluated as highly effective for instructional purposes. It will permit the health science educator to make a rapid, comprehensive search to locate the particular materials most appropriate to his needs.

In FY 1976 the Center will study the latest developments in medical, dental, and allied health professional education as they relate to needs for more effective instructional systems. Close cooperation will continue with other Federal agencies, health professional school faculties, and professional organizations such as the AAMC and the Association of American Dental Schools.

The Center also plans to initiate the development of an integrated series of medical course outlines. These will cover testing, teaching and learning of psychomotor skills, diagnosis of educational problems, and design of appropriate media and facilities. Courses to be offered using these curriculum guidelines will extend the potential reach of workshop programs to all health sciences professional schools.

In an ongoing effort to develop, improve, and evaluate the products of audiovisual educational technology, the Center works closely with the Bureau

of Health Resources Development, HRA. Specific program collaborations have included the production of instructional media for dentistry. Under the auspices of dental professional organizations, dental schools, and government agencies, this project has developed exceptionally effective instructional materials in operative dentistry which are now in use at most dental schools.

Library Operations

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	252	4,743,000	250	4,863,000	-2	+120,000
Other expenses.....	---	5,271,000	---	5,371,000	---	+100,000
Total.....	252	10,014,000	250	10,234,000	-2	+220,000

Library Operations is responsible for selecting, acquiring, indexing, cataloging, preserving and disseminating the world's output of biomedical literature. It provides access to the material through manual and machine produced bibliographies; furnished reference and loan services; prepares and publishes indexes, catalogs, and other publications for use by the biomedical community; and manages a national on-line information retrieval network. It also serves as the Regional Medical Library for the five-state Mid-Atlantic Region, and provides back-up service for the national Regional Medical Library Network as a whole.

The FY 1976 budget request will allow Library Operations to provide basic services at approximately the same level as in FY 1975: acquiring 110,000 serial pieces and 20,000 monographs; indexing 225,000 biomedical articles for inclusion in the computerized MEDLARS data base; publishing 30 recurring bibliographies; binding 32,000 volumes; and providing 176,000 interlibrary loans, 97,000 reader services, 300,000 MEDLINE searches, and 175,000 off-line prints of MEDLINE searches.

In support of the National Cancer Institute, the National Library of Medicine has agreed to add CANCERLINE, an on-line data base of cancer-related citations and abstracts to existing NLM on-line data bases. CANCERLINE data provided by NCI is now accessible via NLM's telecommunications network, thus facilitating worldwide exchange of information on cancer research.

The Library's second generation computerized information system, MEDLARS II, was completed and accepted during the first half of FY 1975. MEDLARS II is a greatly improved and more sophisticated successor to the MEDLARS I system which had been in operation since 1963. Under MEDLARS II a greatly expanded vocabulary capability will make possible improved specificity for retrieving bibliographic information. The system also will provide more rapid access, improved programs for maintaining files, and greatly enhanced on-line retrieval. It stores profiles of users' information needs and provides monthly printouts directly from the computer of the latest literature on these subjects.

In November of 1974 NLM's computer resources were expanded, making possible the extension of its on-line services to a broader segment of the health care community. Beginning in February 1975, direct access to the MEDLINE data base is being made available to over 70 of the largest pharmaceutical and health related chemical organizations. Approximately half of these companies have already been accessing NLM's TOXLINE data base. In addition, the increased resources make possible the further extension of on-line services to local and community hospitals as well as to most of the major Veterans Administration and Armed Forces hospitals.

A use connect charge ($8.00 non-prime time and $15.00 prime time) has been assessed in order to cover the added costs to the Library of providing on-line services. A new billing agreement has been established with the Commerce Department's National Technical Information Service (NTIS) to act as the billing and collecting agent for these services. The fees collected will be used by NTIS to offset the added costs incurred in making equal access and use of the on-line data bases available to any part of the United States. Any excess collections will be returned to the U. S. Treasury.

During FY 1975 the Library renewed its agreements with eight international MEDLARS centers. Such centers have been established in the United Kingdom, Sweden, Germany, France, Canada, Australia, Japan and at the World Health Organization. These agreements have been updated to reflect the expanding capabilities available under the MEDLARS II system. In the past the Library has been receiving quid pro quo in the form of indexing of the foreign literature, which had been an important component of its computerized on-line MEDLARS system. In the new agreements the value of this quid pro quo has been increased from $30,000 to approximately $50,000 per year to reflect the increased capabilities which the MEDLARS II system provides. In addition to the indexing of scientific publications, the foreign centers are providing the necessary keyboarding of indexed material for input into NLM's computerized system. The foreign centers also provide subscriptions to the scientific publications which they are indexing. In addition, they will be providing author abstracts, which are being included for the first time in the MEDLARS data base and which will provide more definitive information to the user. The total value of this cooperative input which the foreign centers are providing is in excess of $400,000. In a number of instances the centers have opted to access the NLM computer directly through the biomedical communications network which now extends to several locations in Western Europe. Because of the time zone difference, such access from Western Europe occurs at different time intervals (3 a.m. to 9 a.m., E.S.T.) than the use requirements for domestic users, and thus does not impair NLM's ability to provide such services in the United States.

NLM has expanded its cooperative cataloging program. Presently, five partners in the United States are contributing to NLM's cataloging data base, and NLM expects to include additional major medical libraries in the future. This will allow the Library to increase the amount of bibliographic and cataloging information announced to the biomedical community through its publication, Current Catalog.

The following are highlights of other major developments in FY 1975-1976: 1) In FY 1975 Library Operations has fully implemented its new INPROC file, which provides management information on acquisition and catalog production. During FY 1976 NLM hopes to make the data base available to the Regional Medical Library network and to book dealers throughout the nation. 2) In FY 1976 the Library will begin to index selected monographic literature for input into the MEDLINE data base. This will provide bibliographic access to individual chapters in addition to the customary entry provided by standard cataloging practices. 3) NLM plans to enhance its bibliographic data base further by entering approximately 100,000 English language abstracts into MEDLINE. This will greatly

augment the utility of a system which already has gained wide and rapid acceptance in the health sciences community. 4) An on-line data base (AVLINE) on selected biomedical audiovisual materials is under development in cooperation with NLM's National Medical Audiovisual Center. Audiovisual material will be cataloged according to NLM cataloging standards and MEDLARS indexing rules. An abstract describing the material will be provided and a printed catalog of audiovisual citations will appear as a section in Current Catalog.

Toxicology Information

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	16	491,000	16	507,000	---	+16,000
Other expenses.....	---	1,339,000	---	1,339,000	---	---
Total.....	16	1,830,000	16	1,846,000	---	+16,000

The Toxicology Information Program (TIP) is responsible for collecting and organizing toxicology data from diverse sources and making the relevant information more readily accessible. TIP obtains information from the published scientific literature and the files of governmental, industrial, and academic organizations; organizes and enters the information into computerized storage and retrieval system; and where appropriate, provides products such as literature searches in specific areas of toxicology.

On-Line Systems

In FY 1975, TIP operated and maintained TOXLINE, its on-line bibliographic retrieval service. The system, which employs the NLM computer and MEDLARS software, achieved a file size of over 350,000 searchable citations, index terms, and abstracts derived from the published literature. The information included data on pesticides, pharmaceuticals, environmental toxins, and hazardous household and industrial chemicals. A use fee of $15 per hour was charged for TOXLINE service, which in FY 1975 produced over 20,000 on-line searches and 145,000 pages of off-line print. This fulfills our commitment to pass on to the user those charges which result from transmission of information from the NLM to the user.

TIP also operated CHEMLINE in FY 1975. This on-line file aids TOXLINE users by providing Chemical Abstracts Service Registry numbers and chemical nomenclature information for substances mentioned in the TOXLINE file. In addition, significant progress was made in building a third on-line retrieval file, the Toxicology Data Bank, covering hazardous chemicals to which it is known that people are being exposed. TIP completed the basic design for this system, began extracting evaluated data from the literature, and entered records on 1,000 chemical compounds into a computer file.

In FY 1976, TIP will enrich the TOXLINE file with additional references in areas of special significance, such as chemicals causing birth defects and cancer. Emphasis will be to service and assist more users from the health services community. Since existing NLM computer resources will limit the size of the TOXLINE file, TIP will reduce the number of years of literature searchable on-line to five and will provide the remainder for off-line batch searches. TIP will continue to operate CHEMLINE and to enhance it with additional on-line retrieval capabilities. The Toxicology Data Bank will be offered as a new on-line service with an initial file covering a broad spectrum of information on 1,000 chemical substances. This new service will allow scientists to coordinate widely differing attributes (e.g., chemical, biological, usage, and manufacturing) of hazardous compounds during on-line search.

Through data exchange agreements worked out under the aegis of the Organization of Economic Cooperation and Development (OECD), several European countries will contribute data in a common format to TIP's data bank, in an experiment on the cost-effectiveness of international collaboration in data base construction. TIP will conduct negotiations with institutions in several foreign countries in order to provide them with access to TOXLINE and CHEMLINE on a quid pro quo basis. In exchange for this service, the NLM will also receive specific toxicology data collected in these foreign countries for use in the Toxicology Data Bank.

Specialized Services and Products

In FY 1975 TIP provided input for the monthly abstract journal and companion tape service, Abstracts on Health Effects of Environmental Pollutants published by Biological Abstracts. TIP assigned Chemical Abstracts Service Registry Numbers to chemicals contained in its own files and those of several other Federal agencies, for the purpose of facilitating the use of such files for toxicology information retrieval. In collaboration with other agencies, TIP is maintaining a table linking the names (and CAS Registry Numbers) of over 1,200 hazardous compounds to the names of the agencies (e.g., NCI, DOT, and EPA) that are interested in specific compounds. The table is being made available to agencies in order to foster interagency coordination in scientific and regulatory activities. The computerized Name-Match system which TIP used in this effort was developed by it in cooperation with the Chemical Abstracts Service and the Computer Sciences Division of the Oak Ridge National Laboratory.

Plans for FY 1976 call for the continued input of selected references from the NLM's MEDLARS data base for the abstract journal. TIP also will provide Name-Match services to other Federal agencies as needed.

Toxicology Information Response Center

In FY 1975, TIP supported the operation of the Toxicology Information Response Center (TIRC) at the Atomic Energy Commission's Oak Ridge National Laboratory. The Center, which partially recovers its operational costs by charging $50 per search, performed over 400 bibliographic literature searches in all areas of toxicology for the scientific community. The Center also sponsored several state-of-the-art reviews on topics of particular current interest in toxicology. The reviews were prepared by selected experts and published in Environmental Health Perspectives or other journals.

In FY 1976 TIP will support the publication of reviews and annotated bibliographies. The emphasis will be on compounds of particular current importance in toxicology such as asbestos, arsenic, vinyl chloride, etc. Through the facilities of TIRC, TIP is establishing an extensive collection of published and unpublished documents on the biological effects of vinyl chloride and related compounds such as chloroprene, vinylidene chloride and epichlorohydrin.

Collaborative Activities with Other Organizations

Under the Toxicology Information Subcommittee of the DHEW Committee to Coordinate Toxicology and Related Programs, TIP carried out its responsibility for coordinating and developing special toxicology information activities in the Department. The initial project to be sponsored under the collaborative effort was a feasibility study to develop a data bank on base line responses in laboratory control animals. This collaborative effort has also involved the establishment of several interagency agreements whereby TIP provides various information services to other agencies.

Plans for 1976 include the continuation of TIP's role in directing the activities of the Toxicology Information Subcommittee and in implementing the system and services identified as needs by this Subcommittee. Information services will be provided to other agencies under cost recovery agreements. These include: (1) a DHEW Toxicology Project Information System, which will help the Department and the agencies in identifying research activities in toxicology carried out under grants, contracts or in intramural projects; and (2) a Toxicology Data and Document Depository which will include (for distribution) toxicology data files and documents that now do not become part of the normal scientific publications system because of format, size or complexity. All systems and services sponsored by TIS and implemented by TIP will be funded through interagency sources via transfer of fund mechanisms.

Research Management and Program Services

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits.....	79	1,975,000	79	2,056,000	--	+81,000
Other expenses.....	--	2,678,000	--	2,655,000	--	-23,000
Total.....	79	4,653,000	79	4,711,000	--	+58,000

This activity provides program management and centralized administrative support necessary for the coordinated operation of all NLM activities. It also manages NLM's international activities funded by the Scientific Activities Overseas Appropriation. Primary functions include the preparation and processing of grant applications for review committees and NLM's Board of Regents; public information and and publications management; financial and personnel management; program analysis and contracts management; administrative services; and coordination of NLM's equal employment opportunity activities. This activity also includes funds for NLM's payment to the National Institutes of Health Management Fund.

NLM has developed an on-line computerized information system which contains data on all grants awarded by NLM. In FY 1975 this data was used for general reporting of program activity and for detailed analysis and evaluation. NLM categorized each grant by program objectives to facilitate measurement of past and future performance. In addition, it undertook formal evaluation of three Medical Library Assistance programs--Regional Medical Libraries, Training Grants, and Medical Library Resource Improvement Grants.

Also in 1975, Research Management and Program Services conducted a workflow study for the entire NLM; performed a major analysis of NLM computer operations; and reorganized the operational arrangements of NLM's biomedical communications network.

In FY 1976 the analysis of data contained in the computerized information system, combined with recommendations from public advisors, will be used to refine statements of grant program objectives. In particular the evaluation of Medical Library Resource Improvement Grants will continue in order to determine the advisability of modifying the program. Over 400 grant applications will be processed.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Medical Library Assistance (Health Services Research, Health Statistics, and Medical Libraries Act of 1974)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	6,333,000	20,000,000	---	6,333,000

Purpose: NLM's programs of Medical Library Assistance provide grants to train professional personnel, strengthen library resources, produce medical reviews, and conduct research in ways of improving information transfer. In addition, contracts provide a network of Regional Medical Libraries with the necessary resources and services to provide backup support locally for medical libraries throughout the United States.

Explanation: Awards are made to individuals directly or to public or non-profit institutions.

Accomplishments in FY 1975: Of the eleven training grants funded in FY 1975, which supported the training of 55 individuals, all but two were in the area of computer applications to medicine.

Biomedical Scientific Publication grants continued to support the preparation and publication of non-profit studies aimed at increasing the availability of information needed by health researchers, educators, and practitioners.

Research grants provided assistance for investigative projects in medical library science, information science, biomedical communications, educational technology, and the history of medicine.

Medical Library Resource grants are designed to assist in the establishment, expansion, and improvement of the nation's health science libraries and to encourage increased financial support for such libraries by the communities in which they are located. In FY 1975 Resource grants emphasized support for cooperative programs in which a strong library undertakes to provide training, consultation, and loan services for small community hospitals and clinics. Regional Medical Library (RML) contracts support a national network of ten Regional Medical Libraries which serve as a backup resource for smaller medical libraries. The number of interlibrary loans made through the RML's in FY 1975 remained at approximately 500,000.

Objectives for FY 1976: In FY 1976, training grants will emphasize the uses of computers in the health sciences. Also in FY 1976 NLM will award approximately 20 Publication grants of which 10 will be new or competing renewals.

Approximately 30 more Research grants will be funded. Potential areas of study include the cost-benefit analysis of computer based information systems; the impact of new information systems on health practitioners; and the development of new information handling systems.

The FY 1976 budget estimate will support the award of 25 Medical Library Resource Improvement grants for core journals and other basic informational materials

needed in community health care institutions. In addition, an estimated 45 Medical Library Resource Project grants will be funded. The grants will continue to complement the NLM's Regional Medical Library program by upgrading the resources of local libraries within each region. In particular, NLM will support formal agreements among local hospitals to promote greater cooperation.

Utilization of the Regional Medical Libraries by the health community is expected to increase substantially in FY 1976 and beyond because health professionals have become increasingly aware of the availability of interlibrary loans; the continued improvement of MEDLINE will afford direct access by RML clients to a data base which is most relevant to health care; and the prohibitively high cost of purchasing literature will force smaller libraries to rely more on inter-library loans from the RML network. The main thrust of the RML program will be in attempting to cope with the expected demand for services while maintaining a high level of quality.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Lister Hill National Center for Biomedical Communications (Public Health Service Act, Title III, Part I, Sec. 381)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
26	2,694,000	Indefinite	23	2,710,000

Purpose: The Lister Hill Center encourages the application of advanced computer and communications technologies to the solution of biomedical information problems.

Explanation: The Center matches high priority needs with technological capabilities to develop experimental services and evaluate their effectiveness and feasibility.

Accomplishments in FY 1975: The Center continued to support an experimental satellite communications network in Alaska utilizing a NASA Applications Technology Satellite (ATS-1). The network, which links remote native villages with Indian Health Service hospitals, has produced a fourfold increase in the number of patients being treated with a doctor's advice. In FY 1975 the Center expanded the ATS-1 remote medical consultation network to support a series of experiments made possible by the recently launched ATS-6 satellite, which has greater capabilities than its predecessor. Five of the ATS-1 voice terminals have been made into operational audio links for the ATS-6 experiments, which already have proven to be a major improvement to the Alaskan biomedical communications network. With the advent of the ATS-6 satellite, the communications network had acquired the capability for two-way live television transmission. Under the Center's direction, satellite telecommunications terminals have been installed and operated in the states of Alaska and Washington to support the ATS-6. Current programs are evaluating the effectiveness of live television consultation between physicians at Indian Health Service hospitals and remote clinics manned by health aides as well as the use of interactive television in support of medical education.

The Center's New England Interactive Television network continued to provide 40 hours of interactive programming per week to between 1,000 and 2,000 viewers at seven institutions. Emphasis in FY 1975 has been on beginning the transition to a fully self-sustaining operation.

Users of the Center's Computer-Assisted Instruction (CAI) network have always had to provide their own computer terminals, communications costs to the nearest access point in the network, and salaries of participating faculty members. In February 1974, users began sharing communications costs more broadly, paying $5.00 per connect hour.

Objectives for FY 1976: The Center will continue its experiments with satellite communications to disseminate medical information among students, practitioners, and research scientists. The ATS-6 Medical education program will be extended to other institutions to provide continuing education for physicians, residents, and allied health practitioners at remote sites.

Although FY 1976 will be the last year of NLM funding for the New England Interactive Network, information produced by the project will be invaluable in planning broadband biomedical communication networks in the future.

The Center plans to test selected Computer-Assisted Instruction programs in the community hospital environment. The experiment in network distribution of particular Computer-Assisted Instruction materials is scheduled to terminate in May 1975. Some 45 of the user institutions have formed the Health Education Network Users Group. This organization will continue to work with NLM and the network contractors to make the transition to a network managed and financed by the users.

The center will be participating with HSA in the creation of a Continuing Medical Education Program for the medical officers of the National Health Service Corps. The Center will support the development of an interactive communication system which, among many other goals, will make possible the acquisition of new information and technical skills in family medicine, internal medicine, pediatrics, obstetrics, and the treatment of trauma. A major objective will be to reduce the degree of professional isolation experienced by these physicians.

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NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: National Medical Audiovisual Center (Public Health Service Act, Title III, Part I, Sec. 381)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
102	2,924,000	Indefinite	100	2,981,000

Purpose: The National Medical Audiovisual Center (NMAC), located in Atlanta, Georgia, applies audiovisual technology to the special needs of biomedical researchers, practitioners, and educators. Its primary mission is to stimulate the development and use of audiovisuals in schools of the health professions and in the continuing education of health professionals.

Explanation: NMAC functions as a clearinghouse for assembling, cataloging, and disseminating information on available instructional media; evaluates, acquires, and distributes materials appropriate for biomedical education; provides consultation and training in the use of instructional audiovisual technology, conducts applied research in instructional technology and systems; and develops prototype instructional media programs.

Accomplishments in FY 1975: NMAC continued to work closely with schools of the health professions and with national professional organizations to identify and develop appropriate instructional media. The Center already has completed significant projects in anatomy, dentistry, and other health science disciplines.

NMAC responded to 3,000 inquires for instructional media information and provided 65,000 film loans and 2,000 videotape duplicates of instructional programs. Technical assistance included 3,000 reports and instructional monographs; 280 site consultations and in-house working sessions; and 15 audiovisual technology workshops. The Center also continued to develop and implement its on-line bibliographic information retrieval system, AVLINE (Audiovisuals on-line).

Objectives for FY 1976: NMAC will study recent developments in medical, dental, and allied health professional education as they relate to needs for more effective instructional systems. Close cooperation will continue with other Federal agencies, health professional school faculties, and professional organizations. NMAC will continue to identify, catalog, and index instructional media for inclusion in AVLINE, which will be made available through NLM's computer and its on-line retrieval network. The Center also plans to initiate the development of an integrated series of medical course outlines. Courses to be offered using these curriculum guidelines will extend the potential reach of workshop programs to all health sciences professional schools.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Library Operations (Public Health Service Act, Title III, Part I, Sec. 381)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
252	10,014,000	Indefinite	250	10,234,000

Purpose: Library Operations is the NLM activity responsible for selecting, acquiring, indexing, cataloging, and preserving the world's output of biomedical literature. It also serves as the Regional Medical Library for the five-state Mid-Atlantic Region and provides back-up service for the national Regional Medical Library Network as a whole.

Explanation: Library Operations provides access to the material through manual and machine-produced bibliographies; furnishes reference and loan services; prepares and publishes indexes, catalogs, and other publications for use by the biomedical community; and manages a national on-line information retrieval network.

Accomplishments in FY 1975: The Library acquired 110,000 serial pieces and 20,000 monographs; indexed 225,000 biomedical articles for inclusion in the computerized MEDLARS data base; published 30 recurring bibliographies; bound 32,000 volumes; and provided 176,000 interlibrary loans, 97,000 reader services, 300,000 MEDLINE searches, and 175,000 off-line prints of MEDLINE searches.

Under an agreement with the National Cancer Institute, NLM added CANCERLINE, an on-line data base of cancer-related abstracts and citations provided by NCI, to existing data bases available through NLM's on-line network. This development should greatly facilitate worldwide exchange of information of cancer research.

NLM's second-generation computerized information system, MEDLARS II, was completed and accepted in FY 1975. A sophisticated successor to the older MEDLARS system in operation since 1963, the new system will make possible much more specific and rapid bibliographic information retrieval.

A use connect charge was assessed to cover the added costs to the Library of providing on-line services. Under a new agreement with NTIS, that agency will act as the billing and collecting agent for these services, with any excess collections being returned to the U. S. Treasury.

NLM renewed agreements with 8 international MEDLARS centers which have been providing NLM with quid pro quo indexing of the foreign literature. In the new agreements the value of this quid pro quo has been increased from $30,000 to approximately $50,000 per year to reflect the increased capabilities which the MEDLARS II system provides. The foreign centers will provide subscriptions to the scientific publications which they are indexing, as well as author abstracts, which are being included for the first time in the MEDLARS data base. The total value of this cooperative input is in excess of $400,000.

Objectives for FY 1976: In FY 1976 TIP will enrich the TOXLINE file with additional references in areas of special significance, such as chemicals causing birth defects and cancer. Since existing NLM computer resources will limit the size of the TOXLINE file, however, TIP will reduce the number of years of literature searchable on-line. The Toxicology Data Bank will be offered as a new on-line service with an initial file covering 1,000 chemical substances.

Plans for FY 1976 also call for the continued input of selected references from the NLM's MEDLARS data base for the abstract journal, Health Effects of Environmental Pollutants. TIP will continue support for the Toxicology Information Response Center for the publication of reviews and annotated bibliographies. The emphasis will be on particularly important areas of toxicology such as asbestos and vinyl chloride. The program also will continue to direct the activities of the Toxicology Information Subcommittee and to provide information services to other agencies under cost-recovery agreements.

Objectives for FY 1976: Basic library services will continue at approximately the same level as in FY 1975. Work will proceed to augment CANCERLINE with information on cancer research still in progress and to increase the number of citations and abstracts in the data base. NLM plans to include additional major medical libraries in its ongoing cooperative cataloging program, thus allowing the Library to increase the amount of information made available to the biomedical community through its publication, Current Catalog. Utilizing the enhanced capabilities of MEDLARS II, NLM will enter approximately 100,000 English language abstracts of biomedical journal literature into the MEDLINE data base. This additional information will greatly augment the utility of a system which already has gained wide and rapid acceptance in the health sciences community. Library Operations will cooperate with NLM's National Medical Audiovisual Center in developing an on-line data base of selected biomedical audiovisual materials (AVLINE). Audiovisual material will be cataloged according to NLM standards and MEDLARS indexing rules, and an abstract describing the material will be provided. In addition a printed catalog of audiovisual citations will appear as a section of Current Catalog.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Toxicology Information (Public Health Service Act, Title III, Part I, Sec. 381)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
16	1,830,000	Indefinite	16	1,846,000

Purpose: The Toxicology Information Program (TIP) is responsible for collecting and organizing toxicology data from diverse sources and making the relevant information more readily accessible.

Explanation: TIP obtains information from the published scientific literature and the files of governmental, industrial, and academic organizations; organizes and enters the information into computerized storage and retrieval systems; and provides products such as literature searches in specific areas of toxicology.

Accomplishments in FY 1975: In FY 1975 TIP continued to operate and maintain TOXLINE, its on-line bibliographic retrieval service. The system achieved a file size of over 350,000 searchable citations, index terms, and abstracts derived from the published literature on topics such as pesticides, pharmaceuticals, and environmental toxins. A fee of $15 per hour was charged for TOXLINE service, which in FY 1975 produced over 20,000 on-line searches and 145,000 pages of off-line print.

TIP also made significant progress in building a Toxicology Data Bank covering hazardous chemicals to which people are presently being exposed. The program completed the basic design for this on-line retrieval system, began extracting evaluated data from the literature, and entered records on 1,000 chemical compounds into a computer file.

TIP continued to provide input for the monthly abstract journal and companion tape service, Abstracts on Health Effects of Environmental Pollutants, and maintained support for the Toxicology Information Response Center at the AEC's Oak Ridge National Laboratory. The Center, which partially recovers its operational costs by charging $50 per search, performed over 400 bibliographic literature searches and sponsored several state-of-the-art reviews on topics of particular current interest in toxicology. The reviews were prepared by selected experts and published in Environmental Health Perspectives or other journals.

As part of the DHEW Committee to Coordinate Toxicology and Related Programs, TIP has helped develop special toxicology information activities for the Department. One of these is a feasibility study for developing a data bank on base-line responses in laboratory animals. The collaborative effort also has led to several interagency agreements under which TIP provides information services to other agencies.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Research Management and Program Services (Public Health Service Act, Title III, Part I, Sec. 381)

1975		1976		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
79	4,653,000	Indefinite	79	4,711,000

Purpose: This activity provides the overall program management and administrative support necessary for the National Library of Medicine. It also manages NLM's international activities funded by the Scientific Activities Overseas Appropriation and provides for NLM's payment to the NIH Management Fund.

Explanation: Primary functions include the preparation and processing of grant applications for review committees and NLM's Board of Regents; public information and publications management; financial and personnel management; program analysis and contracts management; administrative services; and coordination of NLM's equal employment opportunity activities.

Accomplishments in FY 1975: NLM has developed an on-line computerized information system containing data on all of its grant awards. In FY 1975 the data was used for general reporting of program activity and for detailed analysis. NLM categorized each grant by program objectives to facilitate evaluation of performance. In addition, it undertook formal evaluation of the Regional Medical Library program and grants for training and for Medical Library Resource Improvement.

NLM also conducted a workflow study for the Library; performed a major analysis of NLM computer operations; and reorganized the operational arrangements of NLM's biomedical communications network.

Objectives for FY 1976: The data contained in NLM's computerized information system, combined with recommendations from public advisors, will be used to refine grant program objectives. In particular the evaluation of Medical Library Resource Improvement grants will continue in order to determine the advisability of modifying the program. NLM will process in excess of 400 grant applications.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$28,815,000	$6,572,000
Total, obligations	28,815,000	6,572,000

Obligations by Activity

	1976		Interim Period	
	Pos.	Estimate	Pos.	Estimate
Medical Library Assistance				
Total	---	6,333,000	---	870,000
Direct Operations				
Lister Hill Nat'l Center for Biomedical Communications:				
(a) Project Contracts	---	2,025,000	---	495,000
(b) Other Direct	23	685,000	23	170,000
Nat'l Medical Audiovisual Center:				
(a) Project Contracts	---	325,000	---	75,000
(b) Other Direct	100	2,656,000	100	670,000
Library Operations:				
(a) Project Contracts	---	1,920,000	---	480,000
(b) Other Direct	250	8,314,000	250	2,130,000
Toxicology Information:				
(a) Project Contracts	---	940,000	---	250,000
(b) Other Direct	16	906,000	16	225,000
Research Management and Program Services:				
(a) Project Contracts	---	---	---	---
(b) Other Direct	79	4,711,000	79	1,207,000
Subtotal	468	22,357,000	468	5,702,000
Total Obligations	468	28,815,000	468	6,572,000

Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	468	468
Full-time equivalent of all other positions	40	40
Average number of all employees	527	527
Personnel compensation:		
Permanent position	8,506,000	2,120,000
Positions other than permanent	529,000	131,000
Other personnel compensation	117,000	32,000
Subtotal, personnel compensation	9,152,000	2,283,000
Personnel benefits	844,000	209,000
Travel and transportation of persons	160,000	41,000
Transportation of things	24,000	4,000
Rent, communications, and utilities	2,307,000	603,000
Printing and reproduction	369,000	99,000
Other Services:		
Project contracts	5,160,000	1,300,000
Payment to NIH Management Fund	1,696,000	424,000
Other	1,307,000	402,000
Supplies and materials	298,000	72,000
Equipment	1,040,000	265,000
Grants, subsidies and contributions	6,458,000	870,000
Total obligations by object	28,815,000	6,572,000

NARRATIVE

1976 Interim Budget Period

The 1976 Interim Budget estimate of $6,572,000 is a reflection of the National Library of Medicine's commitment to maintain its on-going programs at the FY 1976 level for the same period. The elements of the budget estimate were developed accordingly.

BUILDINGS AND FACILITIES

WITNESSES

LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
ROSS HOLLIDAY, DIRECTOR, DIVISION OF ENGINEERING SERVICES, NATIONAL INSTITUTES OF HEALTH
ROBERT B. LAUDER, JR., BUDGET OFFICER, DIVISION OF ENGINEERING SERVICES, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We now have the National Institutes of Health, "Buildings and facilities" budget request.

The presentation will be made by Leon M. Schwartz, Associate Director for Administration, National Institutes of Health. Your biographical sketch will be included in the record.

Name, Leon M. Schwartz; position, Associate Director for Administration, NIH; birthplace and date, Baltimore, Md., Apr. 26, 1928; education, A.B., economics, Johns Hopkins University, 1950.

Experience, Associate Director for Administration, NIH, January 1972–present; Deputy Assistant Director for Program Management, Research Applications Directorate, National Science Foundation, 1971; Assistant Commissioner for Administration, Office of Education, DHEW, 1968–71; Deputy Assistant Commissioner for Administraion, Office of Education, DHEW, 1967–68; Goddard Space Flight Center, National Aeronautics and Space Administration, 1960–67; Chief of Program Review and Resources Management, 1966–67; Director of Program Support Division, 1965–66; Business Manager, Metrology Satellite Program, 1962–65; Financial Cost Analyst, 1960–62; assistant treasurer and chief accountant, Carpel Inc., 1954–60; part-time instructor, accounting, Baltimore Institute, 1958–63.

Association Membership, Maryland Association of Certified Public Accountants; Federal Government Accountants Association; American Society for Public Administration.

Special awards, citations or publications, Certified Public Accountant; HEW Superior Service Award, 1970; Consultant to National Science Foundation, Advisory Panel for the Research Management Improvement Program, 1973–74.

OPENING STATEMENT

Mr. FLOOD. You have a statement. Do you want to read that?

Mr. SCHWARTZ. Yes, sir.

Mr. Chairman and members of the committee, this appropriation provides funds for design, construction, repair and improvement of facilities for the National Institutes of Health.

In total, we are requesting $3 million in fiscal year 1976 for the following:

Repairs and improvements, plant	$1,000,000
Repairs and improvements, program	2,000,000

In addition, for the interim period budget of July 1, 1976 through September 30, 1976, we are requesting $750,000 for the following:

Repairs and improvements, plant	$250,000
Repairs and improvements, program	500,000

I will discuss each of these briefly.

REPAIRS AND IMPROVEMENTS

Repairs and improvements, plant 1976 budget request $1,000,000, Interim period budget $250,000

These funds are needed for major repairs and improvements to the physical plants at Bethesda, Poolesville, Md.; Hamilton, Mont.; Baltimore, Md., and other field stations for which NIH has the real property holding agency responsibility. The plants are quite extensive and many of the buildings and facilities have been in service over 35 years. The need is a continuing one providing for the care and upgrading of the various mechanical, electrical, and structural systems.

Repairs and improvements, program 1976 budget request $2,000,000, interim period budget $500,000

These funds are requested to continue a source of funding, established in 1975, of financing miscellaneous alterations directly related to program needs which must be characterized as capital improvements. Before 1975, funding of this work had been provided from the operating appropriations of the Institutes. The work includes changes in physical facilities to accommodate revisions and new initiatives in research efforts. Examples of such needs include installation of structural members and restoration of wall and floor areas after the removal of obsolete special equipment which may have penetrated these areas; modification of animal surgery, autopsy, and the like as needed to accommodate expansion of programs such as cardiovascular research; and demolition or relocation of masonry partitions to meet new laboratory layout needs.

I shall be happy to respond to any questions you may have and to supply any additional information desired for the record.

UNOBLIGATED BALANCES

Mr. FLOOD. Last year on page 1,276 of the hearings you estimated that you would end fiscal year 1975 with an unobligated balance of $3,337,000. Now the budget before us states that you will end fiscal year 1975 with an unobligated balance of $8,423,976. How do you account for that difference?

Mr. SCHWARTZ. Mr. Chairman, there have been a number of changes in the time phasing of some of these projects. I can go into it in detail or if you would like I will be happy to provide it for the record.

Mr. FLOOD. Yes; they slipped behind schedule; is that what you are saying?

Mr. SCHWARTZ. Yes, sir.

Mr. FLOOD. And provide the cause of these unobligated funds.

Mr. SCHWARTZ. Yes, sir.

[The information follows:]

As in the 1975 budget, estimates for the 1976 budget were prepared over 1 year ago and a number of unforeseen changes have occurred. Primarily, the reason for an increase in the projected unobligated balance at the end of June 1975 is the result of delays in awarding the construction contracts for projects because of the design phase taking longer than anticipated. An example of this relates to the addition for our central refrigeration plant. Last year we had projected that design of this addition would be completed and the construction contract would be awarded in fiscal 1975. A number of delays in the selection and award of the design contract have caused the award of the construction contract to be postponed until fiscal 1976. This project alone accounts for nearly $3.5 million of the $5 million dollar difference. Another factor is the delay in the settlement of pending contractor claims for completed faciilties. Several buildings were completed and occupied in late 1968 but negotiations are still in process for potential claims of over $500,000. We intend to continue to manage our resources for direct construction projects as conservatively as possible with the best return for the investment.

Mr. FLOOD. How much of the unobligated balance is made up of the figure we appropriated in fiscal 1975?

Mr. SCHWARTZ. We will be utilizing virtually all of those funds. The unobligated balance is largely left over from prior year projects.

TRI-SERVICE INCINERATOR

Mr. FLOOD. Last year, as you mentioned, you did tell us that you were in the process of negotiating the termination costs for that incinerator project. Have you finalized those negotiations with the contractor and if so, how much is it going to cost to terminate that incinerator project?

Mr. SCHWARTZ. We have closed out the project. It will cost a total of $1,500,000.

Mr. FLOOD. How much did it cost to terminate the project?

Mr. SCHWARTZ. I will have to supply that figure for the record.

[The information follows:]

COST BREAKOUT OF TRI-CENTER INCINERATOR PROJECT

Design	$196,280
Cost of awarding construction contracts	11,714
Payments to construction contractors	1,259,113
Total cost	1,467,107

[Clerk's note: The agency stated that it could not distinguish between the costs of services and those to terminate the project.]

Mr. FLOOD. But you did have the total cost?

Mr. SCHWARTZ. Yes, sir.

Part of that included termination charges.

Mr. FLOOD. What are you using now, county facilities?

Mr. SCHWARTZ. The Montgomery County facility is not ready. The county has been in the process of planning it for the year. It is not ready, but we will be glad to participate when it is complete. At the present time we are using the NIH facility. We have for next year's program, some funds to upgrade the facility to make it acceptable to the Maryland State pollution standards.

REPAIRS AND IMPROVEMENTS

Mr. FLOOD. In your statement you said that many of the buildings and facilities at NIH have been in service for over 35 years. Now in your judgment what about this? This is a level of $9 million a year you have for repairs and improvements. Is that adequate for upgrading the various mechanical and electrical and structural systems?

Mr. SCHWARTZ. Actually, Mr. Chairman, the amount available for repairs and improvements is $3 million. It is sufficient for fiscal year 1976. I think in future years this is a cost that will have to increase.

Mr. FLOOD. But I mean right now.

Mr. SCHWARTZ. For 1976 it is sufficient.

Mr. FLOOD. Will you give us a list of projects that you expect to initiate with that $3 million you asked for?

Mr. SCHWARTZ. Yes, sir. I can do it now or supply it for the record.

Mr. FLOOD. You can supply it for the record.

[The information follows:]

INTENDED REPAIR AND IMPROVEMENT PROGRAMS

Examples of the types of projects for which NIH expects to use the $3 million requested in 1976 for repairs and improvements programs include the following: Replacement of a heating boiler at the Rocky Mountain Laboratory, Hamilton, Mont.; and at NIH, modifications to manually operated elevators; installation of a temperature monitoring system; conversion of space for use as animal surgery; and a major consolidation of the patient food service facilities in the clinical center. Other projects include revisions to laboratory areas where the lead time is of short duration.

DESIGNED PROJECTS

Mr. FLOOD. But you do have several projects in which no construction funds were requested at all.

Will you identify, in order of priority, the projects for which all the design work has been completed and indicate the current cost estimates to complete those projects.

Mr. SCHWARTZ. Yes, sir; would you like me to do that now or for the record?

Mr. FLOOD. I would like to hear a few of them.

Mr. SCHWARTZ. Fine.

Certainly the project that Dr. Cummings was discussing with you, the Lister Hill National Center, is a very important project and has a high priority within NIH. I think Dr. Cummings reported to you that the A. & E. drawings are essentially complete and the building will be prepared to go to contract next fiscal year.

We have completed the design work on the Child Health and Human Development Research Facility several years ago. This is a laboratory building that will be used to pull together all of the elements of the National Institute of Child Health and Human Development. You might recall that this is a relatively recent institute within NIH and its intramural programs are scattered throughout the entire campus. This will enable us to pull the program together in a new facility to carry on developmental projects with principal emphasis in the area of reproductive biology. I think you are also aware of the design work that is going on at the National Environmental Health Science Center down at the Research Triangle in North Carolina.

We expect this project to be concluded this year. It will certainly have a very high priority within NIH.

Mr. FLOOD. I was especially interested in the first two you mentioned. You must be a mindreader.

Mr. SCHWARTZ. There is another project I would like to mention and that is the Ambulatory Care Facility which will provide a new dimension to our clinical program at NIH.

Mr. FLOOD. You hang around that campus long enough and a lot of things rub off on you.

LABORATORY ALTERATIONS

Does the building and facilities budget include funds for the laboratory alterations and the renovations of all the NIH Institutes?

Mr. SCHWARTZ. Yes, sir; it does. For all work of a capital improvement nature, I think the committee is aware that this is a new practice for NIH. We used to get the funds directly out of individual appropriations. We now include it in the central account.

Mr. FLOOD. Dr. Rauscher was here and he told us that part of the budget increase for other services was attributed to laboratory alterations and renovations.

Mr. SCHWARTZ. The laboratory alterations that were included in Dr. Rauscher's budget were essentially for the contract-supported work.

The Fort Detrick facility modifications would be included in Dr. Rauscher's budget. There is no duplication in terms of funding for facilities at Bethesda.

BICENTENNIAL ATTRACTION

Mr. FLOOD. One thing I have never been able to understand is that I remember that place out there from the early days. There it is now. This is a fantastic campus as we refer to it, the buildings, Institutes, and clinical center. I never hear in all these advertisements of the tourists coming to town, the visitors go and see this and that, but nobody ever thinks about the fantastic show out there at the NIH operation and how fascinated many tourists would be with the excellent research work you are performing out there.

Of course, it is a little ways out but considering the buses and transportation they come in with, you would think that your PR people, if you have any, would try and sell all these tourist agencies on the idea.

If they had any idea what was there, it would be very exciting. Maybe you don't want them out there. I don't know.

Mr. SCHWARTZ. Mr. Chairman, I am certainly glad you brought that question up at this time for several reasons. This Saturday and Sunday NIH is having its first public open house in 20 years.

Mr. FLOOD. I know about that. You have an alumni association now.

Mr. SCHWARTZ. Yes, sir; that took place this past weekend. I also wanted to mention that in all the Bicentennial information that is being prepared NIH will be listed as a point of interest. We are preparing hopefully for large crowds over the next year. We have some very interesting exhibits set up.

Mr. FLOOD. I am very happy to hear that.
Mr. Conte.

FUNDS NEEDED IN 1976

Mr. CONTE. You expect to have about $8.4 million in unobligated balances as you go into this year. Why so much?

Mr. SCHWARTZ. As we explained in reply to Mr. Flood's similar question, we have had a number of deferrals and some costs which we predicted a year ago to be incurred in 1975 have been delayed until 1976. Although construction funds are provided in a total amount through the buildings and facilities appropriation, we both request and account for these funds on an individual project basis.

Mr. CONTE. Do you really need an additional $3 million?

Mr. SCHWARTZ. The $3 million requested in 1976 is for the exclusive use of our repairs and improvements projects and virtually none of the unobligated balances relates to these projects.

Mr. CONTE. How much of the amount available for obligation do you expect to actually obligate this year?

Mr. SCHWARTZ. We anticipate our unobligated balances at the end of fiscal year 1976, including uncompleted projects and contingenices, to be about $4.5 million. Therefore, we expect to obligate an average of $11 million in both 1975 and 1976.

Mr. CONTE. How much of the money requested will be used on the NIH campus itself?

Mr. SCHWARTZ. The major portion of the $3 million requested for repairs and improvements in 1976 will be used on the NIH Bethesda reservation and the animal center at Poolesville, Md.

Mr. CONTE. Where will the rest be spent?

Mr. SCHWARTZ. The only exception is the use of approximately $125,000 to replace a boiler at the Rocky Mountain Laboratory in Hamilton, Montana.

Mr. CONTE. Do you foresee a need for construction of new research facilities over the next several years?

Mr. SCHWARTZ. There are several facilities which have been designed and for which construction funds have not been appropriated. For example, the laboratory facility for the National Institute of Child Health and Human Development which will consolidate into one facility, research which is now using space intended for other programs and plans are essentially complete for the Lister Hill National Center for Biomedical Communications. We also accord the Environmental Health Sciences Center in North Carolina a very high priority and during this past year we have started the design work for the Ambulatory Care Facility which will provide a new dimension for clinical research at NIH.

Mr. CONTE. What are the factors which determine the need for additional space and the decision to build new facilities to get it?

Mr. SCHWARTZ. Our laboratory facilities are of a special purpose nature, a type which is not available on the commercial market, therefore, program expansion must be in the form of new buildings. Several of these projects are located on the Bethesda Campus and are extensions to already existing Federal facilities.

Mr. CONTE. That is all.

Mr. FLOOD. Thank you, Mr. Schwartz.

Mr. SCHWARTZ. Thank you, sir.

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Justification of the Budget Estimates

Appropriation Estimate

BUILDINGS AND FACILITIES

For construction of, and acquisition of sites and equipment for, facilities of or used by the National Institutes of Health, where not otherwise provided, $3,000,000, to remain available until expended.

For "Buildings and facilities" for the period July 1, 1976, through September 30, 1976, $750,000 to remain available until expended.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation

	1975 Estimate	1976 Estimate
Appropriation	$ 3,000,000	$ 3,000,000
Unobligated balance, start of year	17,517,553	8,423,976
Unobligated balance, end of year	-8,423,976	-4,446,976
Total, obligations	12,093,577	6,977,000

Summary of Changes

1975 Budget Authority	$3,000,000
1976 Budget Authority	3,000,000
Net Change	---

Increases:

A. Program

1. Repairs and improvements, plant	+$1,000,000
2. Repairs and improvements, program	+2,000,000
Total, increases	+3,000,000

Decreases:

A. Program

1. Repairs and improvements, plant	-1,000,000
2. Repairs and improvements, program	-2,000,000
Total, decreases	-3,000,000
Total, net changes	---

Explanation of Changes

Program increases: The $3,000,000 increase includes: $1,000,000 for continuation of the plant repairs and improvements program and $2,000,000 for repairs and improvements for program activities.

Program decreases: The decrease of $3,000,000 is composed of new funding provided in 1975 for: Repairs and improvements for plant facilities and $2,000,000 for repairs and improvements related to program activities.

Obligations by Activity

Page Ref.		1975 Estimate	1976 Estimate	Increase or Decrease
340	Research facilities	$4,314,655	$ 180,000	-$4,134,655
340	Service and administrative facilities	7,778,922	6,797,000	-981,922
Total obligations		12,093,577	6,977,000	-5,116,577

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
NATIONAL INSTITUTES OF HEALTH			
Other services	$11,334,053	$6,917,000	-$4,417,053
ALLOCATION TO GENERAL SERVICES ADMINISTRATION			
Other services	759,524	60,000	-699,524
Total obligations by object	12,093,577	6,977,000	-5,116,577

Buildings and Facilities

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1966	$ 7,781,000	$ 9,431,000	$ 8,977,000	$ 8,977,000
1967	18,279,000	18,279,000	18,279,000	18,279,000
1968	10,715,000	10,715,000	15,075,000	10,715,000
1969	12,495,000	---	5,310,000	---
1970 1/	1,000,000	1,000,000	1,900,000	1,900,000
1971	---	---	---	---
1972	3,565,000	3,565,000	5,065,000	3,565,000
1973	8,500,000	8,500,000	33,480,000	8,500,000 2/
1974	8,000,000	8,000,000	8,000,000	8,000,000
1975	3,000,000	3,000,000	3,000,000	3,000,000
1976	3,000,000			

1/ Prior to 1970, funds include all DHEW health activities. Separate NIH appropriation enacted in 1970.

2/ This appropriation authority was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate amounts in the first vetoed bill.

Buildings and Facilities, NIH

New Obligational Authority	1975 Estimate	1976 Estimate	Increase or Decrease
Research facilities	$ ---	$ ---	$ ---
Service and administrative facilities	3,000,000	3,000,000	---
Total	$3,000,000	$3,000,000	$ ---

General Statement

This appropriation includes all proposed direct construction items of the National Institutes of Health and all continuing projects including unobligated balances remaining from the Mental Health-Neurology Research Facility, which was originally appropriated under "Mental Health Activities" and "Neurology and Blindness Activities" in 1961 but excludes the John E. Fogarty International Center for Advanced Study in the Health Sciences, for which planning funds were appropriated in 1968 under "John E. Fogarty International Center for Advanced Study in the Health Sciences".

Research Facilities

Includes those facilities used directly by the research activities of the National Institutes of Health.

Service and Administrative Facilities

Those facilities which render administrative and service support to the research activities of the National Institutes of Health.

Repairs and Improvements - Plant

1976 appropriation estimate..... $1,000,000

In 1976, $1,000,000 is requested to continue the program of major repairs and improvements to the various electrical, mechanical and structural components of the NIH facilities, many of which have been in service over 36 years.

Repairs and Improvements - Program

1976 appropriation estimate..... $2,000,000

In 1976, $2,000,000 is requested to provide for capital improvements to laboratories and other research facilities which are necessary to adapt them to changes in research procedures, installation of new equipment or new programs.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Program Purpose and Accomplishments

Activities: Research Facilities and Service and Administrative Facilities

1975 Amount	1976 Authorization	1976 Budget Estimate
$3,000,000	Indefinite	$3,000,000

Purpose: The NIH direct construction program provides for the construction, improvement and major repair of the buildings and supporting facilities essential to the conduct of the mission of the National Institutes of Health.

Explanation: Buildings and facilities funded under this appropriation include those required for both research programs and for supportive services at the main NIH reservation, Bethesda, Maryland; the NIH Animal Center, Poolesville, Maryland; the Research Triangle Park, North Carolina; the Rocky Mountain Laboratory, Hamilton, Montana; and other NIH field stations.

Accomplishments in 1975:

Construction Completed

Incinerator - Rocky Mountain Laboratory, Hamilton, Montana
Reproductive and Perinatal Biology Facility

Construction Contracts Terminated

NIH Tri-Service Incinerator Facility

Construction Contracts Continued

Correction of Electrical Deficiencies, Patient Bedroom Areas, Bldg. 10
Electrical and Air Conditioning Improvements, Building 10
Improvements to Blue Collar Work Areas (part)
Master Utilities Extension - Phase II (part)
Modifications to Heating Plant

Design Contracts Completed

Lister Hill National Center for Biomedical Communications

Design Contracts Continued or Awarded

Ambulatory Care Facility
Environmental Health Sciences Center, North Carolina
Improvements to Blue Collar Work Areas (part)
Master Utilities Extension - Phase II (part)
Modifications to Waste Handling Facilities

Repairs and Improvements

Continuation of major repairs and improvements for both plant and program facilities.

Objectives in 1976:

Construction Completed

Correction of Electrical Deficiencies, Patient Bedroom Areas, Bldg. 10
Improvements to Blue Collar Work Areas (part)
Master Utilities Extension - Phase II (part)
Modifications to Heating Plant

Construction Contracts Continued

Electrical and Air Conditioning Improvements, Bldg. 10
Master Utilities Extension - Phase II (part)

Construction Contracts Awarded

Improvements to Blue Collar Work Areas (part)
Master Utilities Extension - Phase II (part)
Modifications to Waste Handling Facilities

Design Contracts Completed

Improvements to Blue Collar Work Areas (part)
Master Utilities Extension - Phase II (part)
Modifications to Waste Handling Facilities

Design Contracts Continued or Awarded

Ambulatory Care Facility

Repairs and Improvements

Continuation of major repairs and improvements for both plant and program facilities.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation

	1976 Estimate	Interim Period
Appropriation	$3,000,000	$ 750,000
Unobligated balance, start of year	8,423,976	4,446,976
Unobligated balance, end of year	-4,446,976	-2,836,976
Total, obligations	6,977,000	2,360,000

Obligations by Activity

	1976 Estimate	Interim Period	Increase or Decrease
Research facilities	$ 180,000	$ 320,000	+$ 140,000
Service and administrative facilities	6,797,000	2,040,000	-4,757,000
Total obligations	6,977,000	2,360,000	-4,617,000

Obligations by Object

	1976 Estimate	Interim Period	Increase or Decrease
NATIONAL INSTITUTES OF HEALTH			
Other services	$6,917,000	$2,060,000	-$4,857,000
ALLOCATION TO GENERAL SERVICES ADMINISTRATION			
Other services	60,000	300,000	+240,000
Total obligations by object	6,977,000	2,360,000	-4,617,000

Buildings and Facilities, NIH

Justification

New obligational authority of $750,000 requested for the interim period of July 1, 1976 through September 30, 1976, represents one-fourth of the 1976 requirements for both Repairs and Improvements - Plant and Repairs and Improvements - Program.

SPECIAL REPORTS

Mr. FLOOD. We have several special reports that were prepared for the committee by the Department of Health, Education, and Welfare. I would like to include the reports in the record at this time.

[The reports follow:]

ACUTE RESPIRATORY DISEASE

Acute respiratory diseases -- caused by viruses, bacteria, and mycoplasma -- are the most frequently occurring illnesses in this country today. Though they cause relatively few deaths -- except in the very young and the very old -- these diseases are responsible for many days lost from school and work -- a loss which has been estimated to cost the Nation more than $5 billion annually.

In addition, repeated viral infections of the upper respiratory tract are particularly serious in persons with chronic lung conditions, such as asthma and emphysema. Indeed, there is a well-founded suspicion on the part of some scientists that repeated acute infections may play a role in the development of chronic obstruction of the airway passages.

Because acute respiratory diseases are so wide-spread, it is not surprising that the cry is frequently heard that Science should "do something about them." The answer is: Science is doing something but the agents causing these diseases are many and elusive. In spite of intensive study, scientists still do not have all the answers needed to bring these infections under complete control.

One of the major goals of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, is to obtain this needed information. Scientists working in Institute laboratories and others supported by NIAID grants and contracts in non-Federal institutions are engaged in a coordinated effort to find better ways to prevent and to treat acute respiratory infections. Other Government agencies with related interests in this field are the Center for Disease Control, the Food and Drug Administration, the Department of Defense, and the Department of Agriculture.

Obligations for programs in Acute Respiratory Disease

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health: National Institute of Allergy and Infectious Diseases.....	$6,305,000	$6,691,000	$7,015,346	$6,664,579	$6,864,516

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Influenza

The Problem. Although man may have been subject to attacks of influenza even in prehistoric times, the historical record of influenza epidemics begins in the 12th century. In each century since then, pandemics (worldwide epidemics) have occurred several times. The last was in 1968-69 and was caused by the so-called Hong Kong flu virus. More than 90 million cases of flu were reported in the U.S. during the six months peak period of this pandemic and there were an estimated 25,000 to 30,000 excess deaths. Because past experience has shown that pandemics generally occur at 10-year intervals, the next world-wide outbreak of influenza is predicted for the late 1970's. By then, however, scientists hope to have the knowledge which will enable them to blunt the impact of "mankind's last great plague."

The Virus. Much new knowledge being accumulated by scientists concerns the human influenza virus. This agent is now known to occur in three immunologically distinct types, A, B, and C. Type B strains cause local outbreaks and epidemics less frequently than A strains while type C rarely causes detectable disease.

The spotlight, therefore, is on type A influenza virus and its ability to change periodically, undergoing minor changes almost every season, and a major modification every 10 to 12 years. When the latter happens, immunity to influenza -- acquired by a bout of flu or a vaccine -- is no longer protective and whole populations once again become susceptible to the new strain.

Few viruses have been more intensively studied than influenza type A. It is now known that its shifty nature is related to changes that take place in two chemical substances -- hemagglutinin (H) and neuraminidase (N) -- found on the outer surface of the virus. When this discovery was made in the early 1960's by NIAID grantees and others, it became possible to identify influenza A virus strains by H and N subtypes and to provide a rational explanation for some of the mystifying relationships long noted between human and nonhuman influenza viruses as well as between strains circulating today and those found in years past.

Vaccines. As scientists have learned more about the influenza virus, its genetic makeup, and its biologic characteristics, this information has been put to use in developing more effective means of protection for at least high risk groups. For example, during the past year, NIAID-supported scientists at Baylor University College of Medicine, Houston, tested an experimental vaccine specific for the neuraminidase antigen alone. These clinical trials showed, as had previous animal studies, that a vaccine aimed at only one component of an influenza virus can prevent illness from and induce resistance to that virus and to non-identical but antigenically similar ones.

The vaccine used in the Baylor trial was a "tailor-made" hybrid developed by Dr. Edwin D. Kilbourne and his associates at Mt. Sinai School of Medicine, New York. The preparation -- called X-32 -- consisted of the hemagglutinin of a horse influenza virus and the neuraminidase of a human influenza virus. Because the horse virus hemagglutinin is non-cross-reactive with human influenza viruses, the investigators (Drs. Robert B. Couch and Julius A. Kasel of Baylor, Dr. John L. Gerin, Molecular Anatomy Program, Rockville Laboratory, Oak Ridge National Laboratory, and Drs. Kilbourne and Jerome L. Shulman, Mt. Sinai) were sure that volunteers receiving the X-32 vaccine would develop immunity to the neuraminidase component only. When these volunteers were exposed to Hong Kong flu virus, it was found that, though infection took place, clinical signs of illness were minimal. Furthermore, re-exposure of volunteers to the Hong Kong virus demonstrated complete protection of X-32 vaccinees who had been infected during the first challenge.

The investigators believe, therefore, that a monospecific influenza vaccine, such as X-32, might improve efforts to prevent the disease. Although natural disease seems to provide rather long-lasting protection, a vaccine made from the currently prevalent influenza virus must be given annually. In contrast, vaccination monospecific for the neuraminidase enzyme allows infection without illness to take place under natural conditions and may allow more durable and more potent immunity to be achieved.

Another NIAID-supported scientist, Dr. Robert Webster of St. Jude's Children's Hospital, Memphis, is investigating the possibility of making an influenza virus subunit vaccine suitable for use in a pediatric population. Studies have shown that various components, or subunits, of the influenza virus, when properly isolated retain the whole virus' ability to induce an immune response, without side effects. Although influenza is a principal cause of childhood croup, during an epidemic the current inactivated influenza vaccines are not recommended for children because of the frequency of reactions, such as fever. Children are not

considered a "high risk" population for influenza but they are important links in the transmission chain and it would be helpful if immunity could be induced safely in school-age children.

During the past year studies have continued on the live, attenuated influenza A virus vaccine developed by Drs. Robert Chanock, Brian Murphy, and others in NIAID's Laboratory of Infectious Diseases. The virus used in this prototype vaccine is a recombinant of the Hong Kong strain and of a temperature-sensitive (ts) mutant of an older strain. The mutant was selected for its ability to grow in the nose and throat and its inability to replicate in the warmer regions of the lungs where it could do harm. This vaccine was tested in various pediatric populations at Children's Hospital, D.C., Vanderbilt University, and the University of North Carolina, and was found safe and capable of inducing an immune response with minimal side-effects.

Emergence of a new strain of influenza virus during the winter of 1972-73 gave the NIAID investigators a chance to apply their ts mutant-recombinant technique to development of a vaccine for the "London flu." This London flu recombinant proved to be safe and relatively effective in stimulating the production of antibodies. There are, however, a number of questions remaining to be answered regarding the genetics and biochemical behavior of the ts mutants. At Rutgers University, Dr. Robert Simpson, working under an NIAID contract, is studying the nature of the ts lesions of various influenza mutants and recombinants. This information Dr. Simpson is seeking should make it possible for scientists to transfer the ts property of a mutant to another virus without affecting the latter's ability to stimulate an immune response.

Other scientists engaged in research on ts mutants of influenza viruses are attempting to develop a laboratory test for degrees of attenuation. There is evidence that the effect of a mutant on the activity of cilia (minute, vibrating, hairlike structures) of cells in trachael organ cultures can be correlated with degrees of virulence of mutants or recombinant influenza viruses. NIAID contractors at Case Western Reserve University School of Medicine, Cleveland, are at present using this information as the basis for a laborstory test for attenuation. Such an assay would be invaluable for selection of future live vaccine recombinants as antigenic drifts or shifts dictate production of recombinants with different surface antigens.

Other Questions. There are numerous questions which remain to be answered on the disease process, epidemiology, and immunology of influenza. NIAID grantees at the University of Florida College of Medicine have established an animal model for the study of host defense mechanisms against influenza infection. They reported last year that ferrets in which segments of the trachea have been isolated and implanted beneath the skin of the neck region can be used to evaluate different host defenses in the same animal. In their studies, Dr. W. Henry Barber and Parker A. Small found that, contrary to their expectations, influenza virus was disseminated from the respiratory tract to the surgically prepared trachael pouch, and vice versa. These events occurred within the first 24 hours after infection and, though the route of dissemination was believed to be the blood, influenza virus antibody administered to the ferrets did not seem to affect this dissemination.

During the past year, NIAID has established at Baylor College of Medicine in Houston an influenza research center where scientists will attempt to find answers to puzzling questions such as those raised by Drs. Barber and Small. The Baylor center, supported by a contract from NIAID, is under the direction of Dr. Robert B. Couch. Assisted by a team of experienced investigators, Dr. Couch will set up studies designed to clarify the influenza disease process and the host immune response. In addition, licensed and experimental vaccines, as well as potential antiviral substances, will be evaluated. In carrying out these studies, the Baylor investigators will have under observation for extended periods different age and social groups.

Some of the questions to which Dr. Couch[4] and his associates will be addressing themselves are: What is the earliest signal of influenza virus activity in a community? What factors influence spread of influenza? What is the disease process in members of different population groups? What is the duration of protection resulting from natural infection or vaccine administration?

During the past several years knowledge of influenza virus infection among animals has expanded at a rapid rate. There is need to intensify epidemiological and epizoological studies to ascertain the significance of animals in the evolution of new pandemic strains. In the near future, NIAID hopes to initiate a contract-supported surveillance system and establish a central laboratory facility for characterizing, cataloging, and banking influenza viruses obtained from animal sources.

RSV, Parainfluenza viruses, and Adenoviruses

In addition to influenza, three other virus families are of special importance in causing acute respiratory illness characterized, in some instances, by flu-like symptoms. These are the respiratory syncytial virus, the parainfluenza viruses, and the adenoviruses.

Respiratory Syncytial Virus. A leading cause of disease in young children is the respiratory syncytial virus. For example, in one study 57 per cent of infants with bronchopneumonia and bronchiolitis -- an inflammation of the lungs beginning in the smaller branches of the bronchial tree -- were found to have respiratory syncytial virus (RSV) infection. Severe bronchiolitis occurs almost exclusively in those less than one year old and bronchopneumonia in older children.

Deaths from these conditions occur most frequently among infants less than one year. For this reason, attempts to develop an RSV vaccine have focused on a preparation which would be both safe and effective in this age group. Some years ago, NIAID scientists and others attempted to protect children from RSV infection through use of an inactivated RSV vaccine. Although the vaccine induced high levels of what should have been protective antibody, infants given the vaccine dedeveloped more frequent and more severe lower respiratory tract illness than did nonvaccinated children of the same age. Attempts shifted, therefore, to development of a live vaccine using a ts mutant which, like its influenza counterpart, would not grow in the lower respiratory tract.

Two years ago, Dr. Robert Chanock of the Laboratory of Infectious Diseases, NIAID, developed a promising ts mutant of the RS virus. When this mutant was tested as a vaccine in older children, however, it showed signs of reverting to the unmodified or "wild type".

Recently, "double" mutants to RSV have been developed both by Dr. Chanock and by Dr. Robert Simpson at Rutgers. These double mutants are viruses that have been mutagenized twice, thus making it less likely that they can revert to their original form. Some of these double mutants will be used as seed viruses for the preparation of vaccines by Flow Laboratories, Inc., Rockville, Md., which serves as a contractor for the preparation and safety-testing of potential NIAID vaccine pools.

Parainfluenza Viruses. These agents are a common cause of pharyngitis, bronchitis, croup, and bronchopneumonia in children and an occasional cause of upper respiratory infection in adults. Four types of paraflu viruses are responsible for at least 1/3 of the cases of croup in children admitted to hospitals. Croup caused by these viruses is very severe and occurs most frequently between the ages of 1 and 4 years. The disease spreads rapidly among young children in institutions and family groups. At present Dr. Simpson at Rutgers is attempting to isolate double mutants of parainfluenza viruses for possible use as vaccines.

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Adenoviruses. There are 32 types of human adenoviruses but only certain ones seem to be agents of highly prevalent disease in man. Types 4 and 7 are of major importance in causing respiratory illness in military recruits, and types 1, 2, and 5 are important causes of acute respiratory diseases, including pneumonia, in children.

Oral vaccines using live virus have been developed by NIAID scientists and contractors for adenovirus 4 and 7 and have been successfully used by the military. However, several adenovirus strains are known to cause tumors when injected into newborn animals. This finding remains a point of concern, although recent studies have failed to support a role for adenoviruses in human tumor formation.

Recent development of methods for isolating and crystallizing antigenic structures on the surface of the adenovirus has provided the opportunity to develop subunit vaccines completely free of nucleic acid and, therefore, with no tumor-forming capacity. Moreover, such preparations have no detectable extraneous, non-viral protein, a feature which should eliminate side effects, such as a sore arm following the injection of vaccine.

Two subunit vaccines for type 5 have been prepared through collaborative efforts of Dr. Julius Kasel, formerly of NIAID, now at Baylor, and Dr. H. G. Pereira, Mill Hill, England. Both vaccines have been shown to be antigenic (capable of inducing protective antibodies) and safe in adults and teen-agers. They are now being evaluated, under contract at the Baylor College of Medicine, in younger children.

Dr. Kasel has also prepared two subunit vaccines of adenovirus type 4. These will be tested in adults in order to ascertain their antigenicity.

Bacterial Vaccines

Other organisms of particular concern in causing serious acute respiratory disease include Diplococcus pneumoniae and Mycoplasma pneumoniae.

Pneumococcal pneumonia (caused by Diplococcus pneumoniae) continues to result in considerable sickness and perhaps as many as 45,000 deaths annually in the United States. In spite of the availability and use of effective antibiotics, the 20 to 30 percent fatality rate of patients hospitalized with pneumococcal pneumonia has remained unchanged over the past decade. For this reason, efforts to diminish the effect of the pneumococcus organism are focused on development of vaccines for use in "high risk" groups. These have been identified as persons over 50 years of age or with chronic illnesses.

Although the pneumococcal organism occurs in more than 82 distinct types, only 14 of these are implicated in the majority of pneumococcal infections. Therefore, the proposed vaccines will be polyvalent (more than one type per vaccine) and will include the types that have been most frequently isolated from patients with bacteremic pneumonia.

Most of the work supported by NIAID on pneumococcal vaccine development and the epidemiology of pneumococcal infection has been carried out under contract with the University of Pennsylvania and Dr. Robert Austrian, the principal investigator. A vaccine trial using two hexavalent (6 types) vaccines was initiated in January 1973 at Dorothea Dix Hospital, Raleigh, North Carolina. Approximately 64% of the over 1,000 participants in the study are 50 years of age or older. Rather minor adverse reactions were observed and, as a group, the vaccinees responded well to each of the 12 total antigens. These vaccinees will be followed for development of pneumococcal infection.

A large-scale trial is underway to determine the efficacy of a dodecavalent (12 types) pneumococcal vaccine in preventing type-specific pneumococcal pneumonia

and total respiratory disease in adults over age 45. The study is being carried out in San Francisco under an NIAID contract with Kaiser Foundation Research Institute. Immunizations began in January 1974 and nearly 12,000 people have been entered into the study.

M. pneumoniae. Mycoplasmas are the smallest of free-living organisms capable of reproducing themselves without assistance from other forms of life. They are similar to bacteria in many ways but lack a rigid cell wall. For this reason they are resistant to penicillin and other antimicrobial agents that act by interfering with cell wall synthesis.

Although mycoplasmas are found in many species of plant and animal life, M. pneumoniae is the only member of this large famtly known to produce respiratory disease in man. Primarily affecting older children and young adults, the organism is spread by close contact, particularly within families, institutions, and military units. The most serious manifestation of infection in man is what is known as "atypical pneumonia."

During the past few years an inactivated M. pneumoniae vaccine has been developed by NIAID contractors at Ohio State and Cornell Universities and tested for safety and potency at the University of Virginia and Baylor University. A new contract has recently been awarded investigators at the University of Virginia to study the clinical acceptability, antibody response, and efficacy of the inactivated vaccine. Dr. Richard P. Wenzel, the principal investigator at Virginia, first found that the vaccine was acceptable in regard to serum and nasal antibody production in 20 volunteers at the University and in approximately 150 incoming Marine Corps recruits at Parris Island, South Carolina. An efficacy study in 7,500 volunteers has now been initiated at Parris Island.

In the meantime, scientists in NIAID's Laboratory of Infectious Diseases are attempting to develop ts mutants of M. pneumoniae which would be suitable for use as vaccine strains. One, called ts-H43, is particularly promising. The scientists were pleased during the past year to find that ts-H43, when given volunteers via the intranasal route, greatly increased the production of IgA, or secretory, antibody. This antibody -- which is found in various body secretions, particularly those of the nose and throat -- is believed to play an important role in protecting a person against M. pneumoniae disease. A cautious expansion of trials with this mutant is planned in larger numbers of volunteers.

Although several attempts to use ts mutants of respiratory viruses have been encouraging -- as in influenza and RSV -- the NIAID scientists are the first to apply this technique to free living organisms. Their promising results with M. pneumoniae may offer a new approach toward the control of other bacterial respiratory pathogens.

Outlook

A promising approach to control of acute respiratory disease is the development of effective anti-viral drugs. Progress in this field was reviewed by scientists attending the Eighth Influenza Workshop held in December 1974 at the National Institutes of Health and supported by the NIAID. Since vaccines are not completely effective in preventing acute respiratory disease, the search is on for chemical agents which might be used for protection or treatment.

One drug -- Amantadine -- has been licensed for use in preventing illness from susceptible strains of the influenza A virus. At the workshop, studies were reported on the drug's pharmacology, toxicity, and clinical use. Although this drug has been available for some time it has not been as widely used as some physicians think it should be. There was general agreement at the workshop that Amantadine is effective against current influenza A strains and that there is hope that it will also be useful against the one which may next emerge.

An interesting aspect of Amantadine's action is its augmentation of the protective effect of live vaccines. Several investigators have reported that serum antibody levels are higher in volunteers given both vaccine and the drug than in those given either alone. At the Influenza Workshop one investigator suggested that, in the face of an outbreak of influenza, members of the population might be both vaccinated and given Amantadine, since it is assumed that the drug, which goes to work right away, could provide some protection until vaccine-induced antibody reached effective levels.

Even when Amantadine fails to prevent influenza, it seems to ameliorate the usual symptoms of the disease. Fever is lower and there are fewer "aches and pains." This is true, however, only when the drug is given in advance of infection. Its usefulness after the virus has taken hold is debatable. In animal studies, however, it has been found to increase survival and a suggestion was made at the Workshop that more studies are needed on the ability of Amantadine to prevent serious illness.

Although physicians would, naturally, welcome anti-influenza drugs, they are even more anxious to have compounds available for use in preventing or treating the common cold. This illness is caused by viruses so many and so varied that a broad-spectrum antiviral agent seems to offer the best hope for control.

NIAID-supported research in this area has focused on interferon -- a natural substance produced in the body in response to viral, and other, infection. Efforts are being made to increase the amounts of interferon produced, through the use of a chemical inducer, or to apply interferon that has been prepared in cell cultures. Although there has been encouraging progress, neither of these approaches has yet been entirely successful in providing a practical means for preventing or treating the common cold.

But a number of other products are being evaluated: calcium elenolate, Ribavarin, CP-20,961, Tilorone. These are some of the chemical compounds presently being tested against acute respiratory viruses. Information on their effectiveness is still sketchy and contradictory. But eventually one of these drugs may take its place in the family medicine cabinet or the doctor's bag as an effective antidote for the colds and flu-like-illnesses that plague man around the world.

ARTHRITIS, RHEUMATIC DISEASES, AND RELATED DISORDERS

The arthritic diseases, rheumatism, and related bone and connective tissue disorders afflict more than 18 million people in the United States, at a cost of about $4 billion to the nation annually. The most prevalent form of arthritis is degenerative joint disease, known as osteoarthritis; more than half of all people beyond the age of 55 exhibit such degeneration. The most severely crippling form of rheumatic disease in younger age groups is rheumatoid arthritis, which afflicts about 5 million Americans. Each year, however, important steps are taking place in understanding and controlling these diseases, largely as a result of extensive biomedical investigations, both at basic and applied levels of research, conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Obligations for Programs in Arthritis

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases	$14,374,000	13,808,000	17,116,000*	13,171,000	13,921,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Arthritis, the oldest known chronic disease, remains today the most prevalent crippler in the United States. About a hundred distinct disorders are represented in the classification "arthritis and rheumatism," of which more than a dozen are considered serious public health problems, notably rheumatoid arthritis, juvenile rheumatoid arthritis, degenerative joint diseases, systemic lupus erythematosus, and gout.

These diseases result in unemployment equivalent to the loss of about half-a-million people in the United States each year. The government will spend more than a billion dollars in disability payments to individuals crippled by arthritis during this decade. The estimated overall cost to individuals and government has been placed at $4 billion yearly.

Research continues to improve treatment of arthritis. Substantial progress is being made in the areas of basic research in the fundamental disciplines which enhance understanding of rheumatic disorders. Investigators and grantees of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) are developing basic information to elucidate problems of inflammation and tissue destruction characteristic of these diseases and the immunologic mechanisms that, in some instances at least, initiate and perpetuate these processes.

* Includes $3,040,000 in 1974 from the release of 1973 impounded funds.

RHEUMATOID ARTHRITIS

This form of arthritis afflicts about 5 million people in the United States. Although investigation has provided more effective ways of limiting the associated pain and deformity, the cause of this crippling disease remains obscure. An important guide in the continuing search comes from recognition that the underlying abnormality is not limited to joints but may affect any organ of the body. For example, NIH grantee Dr. Robert Turner and associates at the Bowman Gray School of Medicine at Winston-Salem, North Carolina, have added to knowledge of cardiac involvement in this disease, making use of echocardiography, a method of reflecting ultrasonic sound from heart structures.

The mechanism at work in causing this widespread chronic inflammation involving various systems of the body is believed by many investigators to be an abnormal reaction of the body's immune system, a reaction stimulated by infection or a misdirected attack by the body's defense systems on its own tissue (an autoimmune reaction). A mechanism of this kind, with varied trigger factors, agrees well with what is known of the natural history of this disease. Although a number of infectious agents have been isolated from tissues of patients with rheumatoid arthritis, none has been identified as a definite cause of the disease.

A novel approach to this important line of inquiry has been taken by Institute grantees, Dr. Norman L. Gottlieb and associates at the University of Miami School of Medicine. They conducted an epidemiologic survey of pet ownership (dogs, cats, and birds) in patients with rheumatoid arthritis. Using groups of patients with other forms of arthritis and non-arthritic disease for comparison and directing their inquiry to the five year period preceding the onset of arthritis, these investigators found in the rheumatoid arthritis group a significantly higher prevalence of pet ownership. Although these findings seem to lend support to the hypothesis of an infectious causative factor in rheumatoid arthritis, the limited size of the study and the need to consider alternate explanations such as hypersensitivity to fur or feathers, are factors to be considered in interpreting the results. Additional research appears warrented since it is known that pets harbor a wide variety of infectious organisms which are known to produce human disease.

Mechanisms of Immunity Under Investigation

Numerous studies have demonstrated an approximate correlation between the severity of rheumatoid arthritis and the presence of rheumatoid factor in the blood. In some patients with rheumatoid arthritis, however, this factor is lacking, making diagnosis and classification more difficult. Now, recent studies pointing to the involvement of the complement system, a major link in the body's immunological responses, have been shown to be of value in this respect particularly in those patients who are serologically negative for rheumatoid factor.

Determination of complement in fluid recovered from inflamed joints has been shown to be helpful in evaluating rheumatoid arthritis patients. In recent studies, Dr. Frederic C. McDuffie and his associates at the Mayo Clinic, Rochester, Minnesota, were able to identify four groups from among 62 patients with rheumatoid arthritis on the basis of the presence or absence of serum rheumatoid factor and low or normal joint fluid complement levels. The relationship between joint fluid complement levels and the severity of rheumatoid arthritis was studied by comparing clinical, laboratory and X-ray tests with results of similar measurements in control patients. This has added to our knowledge in two ways, first, by showing that joint fluid complement determination can be used to diagnose and classify patients with arthritis, particularly in the absence of rheumatoid factor in the blood, and second, the finding of low complement levels in joint fluid is consistent with the hypothesis that immunologic factors--specifically an antigen-antibody reaction within the joint that utilizes complement--play an important part in the development of rheumatoid arthritis.

An Institute grantee at the University of California, San Diego, Dr. Nathan J. Zvaifler, has conducted research which demonstrates that the complement sequence--a series of events in which a group of blood proteins interact to initiate inflammation--contributes significantly to the progressive destruction of joints that is characteristic of rheumatoid arthritis. He concludes from his studies that antigen-antibody complexes are responsible for activation of the complement sequence.

In addition to the work on proteins active in immune reactions, important evidence for operation of immune mechanisms in these diseases comes from study of the immune cells.

Of great importance to establishing a link between immune mechanisms and rheumatoid diseases is the finding by Dr. Paul Terasaki and associates at UCLA that most patients with ankylosing spondylitis possess a common genetic cellular factor (histocompatability antigen) present in only a small percent of the general population. The association of the disease with such a factor suggests that some aberrant, genetically controlled, cellular immune response may be the cause. Such factors first came under study in the search for tests of compatibility between donor and recipient in the transplantation of organs like the kidney. The finding of an association between compatibility factors and disease is a good illustration of how unpredictable the path of discovery can be.

Cells known as B-lymphocytes play an important role in the inflammatory reaction of tissue in individuals with rheumatoid arthritis. An Institute grantee, Dr. Morris Ziff of the University of Texas Southwestern Medical School, after observing large numbers of cells from rheumatoid arthritis joint membranes under the electron microscope, suggests that immune responses occur both in the joint fluid and in joint tissue. Such studies sustain the long-standing search for an infectious agent in rheumatoid arthritis. Institute scientists and grantees continue to search for viral agents associated with rheumatoid arthritis. Investigators have tested the susceptibility of cells taken from rheumatoid patients to numerous viruses, but so far no concrete evidence has been found demonstrating a viral trigger.

Treatment of Rheumatoid Arthritis

The program of treatment in the early stages of rheumatoid arthritis is designed to relieve pain, to control inflammation and to prevent deformity. Many cases can be controlled satisfactorily on a program of rest and physiotherapy, utilizing salicylate drugs such as aspirin. In some cases, the disease subsides without intervention. In other cases, progressive joint damage may not be stopped or slowed down with rest and salicylates, or the process, having subsided, may flare up with any attempt to resume normal activity. The physician has available a wide range of alternative drugs which, although they may be more effective in controlling the disease are also more likely to have toxic side-effects. The list includes gold salts, corticosteroids, chloraquine, penicillamine, and the immunosuppressive agents. Because of the toxic effects of these drugs, those who administer them must follow strict guidelines exploring the safest therapy first, restricting use of the most hazardous to cases with life-threatening complications or potential for serious crippling. Meticulous follow-up with monitoring for toxic effects is mandatory. Continuing research in this area constitutes a major aim of both intramural and extramural programs of the Institute.

Research by Dr. Morris Ziff and Dr. Eric R. Hurd at the University of Texas Southwestern Medical School has confirmed the efficacy of the immunosuppressive drug cyclophosphamide in treating rheumatoid arthritis. They are investigating the mechanism of action as well. The investigators found that clinical improvement correlates well with reduction in numbers of monocytes and small-lymphocytes, in the blood of treated patients. This observation provides both a means of monitoring treatment and a clue to the mechanism of drug action.

Recently, an Institute grantee, Dr. John T. Sharp and associates of the Baylor College of Medicine showed by radiologic evaluation that gold therapy beneficially altered the course of rheumatoid arthritis in a group of patients given weekly gold injections for 22 weeks and maintenance injections at increasing intervals for two years. Periodic radiologic examination showed arrest of bone and cartilage destruction in several patients and a significant slowing of the progression rate of joint damage for the treated group.

Corticosteroid drugs, despite the dramatic relief they sometimes provide, do not alter the course of rheumatoid arthritis. Even small doses given for prolonged periods can result in serious clinical complications, e.g. bleeding from peptic ulcer or loss of calcium from bones. A recent study by Institute grantee Dr. Louis V. Avioli and his associates at the Washington University School of Medicine, St. Louis, has shown a similarity in the pattern of bone loss resulting from corticosteroid therapy with that observed in primary hyperparathyroidism. The researchers suggest that patients receiving chronic corticosteroid treatment may experience bone loss as a result of elevated parathyroid hormone levels. The increased level appears to be secondary to decreased intestinal calcium absorption. Preliminary studies indicate that the process can be reversed by administration of vitamin D which acts to increase intestinal calcium absorption.

In view of the problems created by administering drugs, great interest attaches to treatment based rather on removing a harmful agent. Surgical removal of the thickened connective tissue so conspicuous in diseased joints of the individual with rheumatoid arthritis - synovectomy - was first introduced as an aid in the treatment of advanced cases, but is now coming to be used in earlier stages of the disease. Studies conducted at the NIH Clinical Center and elsewhere confirm the finding of reduced inflammation and improved function; they suggest, too, that to remove the inflamed tissue is to remove the agent active in destruction of the joint.

Search for remedial agents and for understanding of the disease

Understanding of a disease process generally provides a valuable guide to the search for effective remedial agents. The limited understanding of rheumatoid arthritis, however, has meant that search for such agents must proceed largely through a trial and error process. Once successful agents are found, they become the focus of intense investigation, and understanding the mechanism by which a newly discovered treatment produces its effect hopefully leads to fresh perspectives on this elusive disease. Thus Drs. Stephen Malawista and Daniel Wright, Institute grantees at Yale University report that the anti-inflammatory effects of colchicine, long recognized as very effective in relief of the acute arthritis of gout, acts by preventing release of destructive enzymes from white blood cells. Release of these enzymes, normally stored as intracellular particles or "lysosomes," may well be the final common path in production of cartilage destruction and connective tissue overgrowth. This inquiry into the cellular response to colchicine thus establishes a valuable link between old, well-tested knowledge of treatment and understanding of disease mechanisms provided by new knowledge of cellular metabolism.

Another empirical approach to treatment now being examined from the perspective of new knowledge is that of aiming for prompt control of inflammation. A fresh vantage point is being provided by the observations of Dr. Edward D. Harris, Jr., Institute grantee at Dartmouth University, on variation in collagen destruction with temperature. He found the enzymatic destruction of collagen fibrils, one of the key structural components of joints, proceeds at a much faster rate at the elevated temperature characteristic of inflammation (34-37.6°C). Collagen breakdown was as much as four times greater than at temperatures characteristic of normal joints (30.5-33°C).

This finding raises questions concerning treatment of inflammed joints with induced heat (such as diathermy). Such treatment may increase internal joint temperatures and may actually aggravate the inflammation and joint damage through stimulation of collagen destruction. Dr. Harris' work suggests that part of the benefit from anti-inflammatory therapy in rheumatoid arthritis may be secondary to lowering the internal temperature of the affected joints, thereby decreasing the rate at which collagenase degrades cartilage collagen. His finding provides one explanation of the mechanism of effective local suppression of joint inflammation by intra-articular injection of steroid drugs.

This new insight into the mechanism of tissue destruction comes as a direct outgrowth of research on the change from tadpole to frog where Drs. Jerome Gross and Charles Lapiere demonstrated that a collagen-destroying enzyme had a role in dissolution of the tadpole's tail. Working with Dr. Gross, Dr. Stephen Krane succeeded in demonstrating the presence of such an enzyme in human tissues and the destructive effects of this enzyme on joint structures. It was then, in collaboration with Dr. Krane, that Dr. Harris embarked on the study of temperature dependence of the destructive effects. The sequence from tadpoles to temperature effects has been supported by a combination of research, training and Research Career Development awards extending over more than a decade.

Arthritis with deformity as seen in children presents features that mark it as a separate disease, particularly when high fever and skin eruption are present without the elevation of rheumatoid factor so characteristic of adult rheumatoid disease. The observations of Dr. Paul Terasaki on the prevalence of a genetically determined cellular factor (histocompatibility antigen W27) in both adult and juvenile forms of arthritis have, however, demonstrated a link between them. Such evidence suggests that there is a common origin to various arthritic diseases, such as inherited susceptibility to infectious agents which are yet to be identified.

OTHER CONNECTIVE TISSUE DISORDERS

Systemic Lupus Erythematosus

Another connective tissue disorder in which the Institute supports research is systemic lupus erythematosus (SLE), a chronic inflammatory disease of unknown origin which may affect several organs, the joints, lung, spleen, heart or kidney. It affects some 50,000 new victims each year, particularly women between 20 and 40 years of age. Considerable evidence indicates that SLE, too, may be a disorder of the immune mechanisms of the body, and that it may be triggered by an infectious process although sometimes the disease appears as a reaction to certain drugs. Investigators at the NIH Clinical Center in Bethesda are, therefore, studying the effects of the immunosuppressive agents cyclophosphamide and azathioprine in efforts to control the immune system and thereby the disease process.

Institute grantee Dr. Frederic C. McDuffie and associates at the Mayo Clinic have reported for the first time involvement of immune complexes and complement in the onset of pericarditis in association with SLE. The investigators believe that measurement of complement in pericardial fluids may be helpful in diagnosis of certain pericardial conditions, SLE, and other diseases involving an immune-complex mechanism.

Osteoarthritis

Osteoarthritis (degenerative joint disease) is a common, severe disability that appears to be the result of the erosion and disorganization of joint tissues that generally accompany the aging process. Within the heterogeneous category of degenerative arthritis, different

factors can be recognized as being responsible for the accelerated deterioration. These include the unusual wear experienced by those with deformity or obesity and early degenerative changes with a strong familial history of occurring at such specific sites as the terminal finger joints or the hip. Efforts in preventing unusual wear are critical where deformity or obesity is involved and for early degeneration of genetic origin new developments in joint replacement, as described under Orthopedics, now enable many to return from wheelchair existence to an active life.

Gouty Arthritis

More than a half million Americans, nearly all of them men, have gout, a hereditary disorder of purine metabolism. In this disorder, uric acid, a breakdown product of purines, themselves products of protein metabolism, is deposited under the skin or in and around the joints in the form of the salt, sodium urate. These salt crystals may cause excruciating pain and if treatment is not initiated, the deposits will grow. Eventually these deposits may form distinct masses which bring about permanent destruction of the joints and crippling. Uric acid stones may form in the urinary passages and lead to impairment of kidney function.

Of the common joint disorders, gout responds most favorably to treatment. Past research, to a large extent conducted and supported by the Institute, led to elucidation of the basic mechanisms of the disease and to study of new drugs, such as allopurinal, which counteract uric acid synthesis and buildup in the body, and other drugs which stimulate renal excretion of uric acid. Institute investigators are pursuing a number of leads relates to the underlying cause of gout and the manner by which typical gouty inflammation is produced.

BONE DISEASES AND ORTHOPEDIC RESEARCH

The Institute mission in bone disease is served by several Institute programs, notably, connective tissue metabolism (in the arthritis program) as it related to bone matrix, tendons, ligaments, and wound healing, and calcium metabolism, including investigation of nutritional factors and endocrine regulation in the supply and distribution of this critical element. A growing contribution to the Institute's mission in diseases of bones and joints comes from investigations originating with concerns of the orthopedic surgeon. Recent developments in development of artificial joints provide an instructive example of this contribution.

Development of specific artificial joints - shoulder, elbow, finger, hip and knee - and methods for attachment of these joints to bones, tendons, or muscles is a major interest of orthopedics research. Successful transplants at natural joints are dependent upon a better understanding of the graft-rejection process, bone immunology, bone metabolism, fracture healing, skeletal attachment, skeletal-soft tissue trauma, and other factors in the healing process. Research in these areas in under way. Many of these efforts involving connective tissues and cartilage are directed toward a better understanding of biochemical structure, ultrastructure, genetic factors, and enzymology of these tissues, as well as to the process of tissue-skeletal repair.

Interest in implantable materials has brought a recent influx of engineers and polymer and ceramic chemists into biomedical research.

Studies are under way to determine the best materials for fabrication of joints that will display minimal antigenicity and toxicity, maximum acceptance by the body and will also exhibit little wear or corrosion. Materials with these characteristics will enable the joint to remain securely attached to the skeletal or muscular system and will not necessitate replacement throughout the lifetime of the patient.

Total Replacement of the Hip

Hip joint replacement has proven to be one of the most successful orthopedic procedures in restoring mobility, even in many cases where previous reconstructive surgery has failed. The Institute provides grant support to several researchers performing and evaluating total hip replacement at centers throughout the United States.

The artificial hip is probably the most advanced of the artificial joints under study. Imperfections still exist in the materials used to fabricate the joint and in methods of attachment. Researchers are presently working with carbon reinforced plastics and ceramics, TRIP steel (which is an alloy of steel, chromium, and nickel), and other metals. Porous metals and metals coated with porous ceramics or plastics are being used in an effort to obtain implant attachment through ingrowth of tissue into the pores of the implant. Many of the materials now in use promise adequate durability for most older patients. Surgeons suspect, however, that the plastic socket now used may eventually have to be replaced in patients who received their implant when younger. The outlook for replacement of joints of all kinds in the treatment of arthritic conditions is rapidly improving. Within the next few years, it is expected that prostheses with increased wear characteristics and cements which are more compatible with human bones will be developed.

Bone Research

NIAMDD grantee Dr. Ali Seireg at the University of Wisconsin is conducting research on the effects of stress on bone mineral content, the role of muscle fatigue in fracture, and the cause of wear in joints. By analyzing the bones of rats subjected to an exercise program, Dr. Seireg has found that frequency and magnitude of stress applied to the leg changes bone size and mineral content and, therefore strength. While stress and exercise lead to increased bone strength, excessive exercise also leads to damage in the joints. Like bone, cartilage increases in mineral content when it is under stress. Dr. Seireg has found that as exercise calcifies the cartilage, the joint stiffens and the stress distribution becomes uneven, making the cartilage corrode more rapidly. Degradation of synovial fluid, the lubricant in joints, also causes cartilage to become worn. The investigator has found that the body cannot rejuvenate synovial fluid quickly enough when exercise is too great. As the synovial fluid breaks down, the temperature in the joint rises. Joint temperature is thought to be useful as a tool for measuring damage in joints, and is one of several techniques researchers have developed for testing drugs and treatment methods for arthritis caused by excessive stress.

OUTLOOK

The studies mentioned here are included in the 150 ongoing research efforts supported by grants or conducted in the NIH laboratories in Bethesda in the area of arthritis, rheumatic diseases, and related disorders. This research is illustrative of the Institute's commitment and of recent progress. This continuing effort is constantly improving treatment, understanding and control of these diseases, while increasing the foundation of basic scientific knowledge which could lead to an eventual cure or prevention of these disorders.

CLINICAL IMMUNOLOGY: ALLERGY AND ORGAN TRANSPLANTATION

In the past decade, clinical immunology has emerged as a recognized specialty dealing with disease states that require stimulation of immunity, correction of immune deficiencies, and elimination of undesired immune reactions. By manipulating the immune response, scientists are making significant progress in diagnosis, treatment, and prevention of disorders affecting almost every system of the body.

The role of immunology in infectious diseases has been amply demonstrated through the development of many effective vaccines. In addition, there are increasing indications that immunology may play a role in other diseases, including cancer, multiple sclerosis, rheumatoid arthritis, and complications of aging.

This report, however, concentrates on the application of immunology findings in just two fields: allergy -- where the immune reaction to a foreign substance is harmful; and organ transplantation -- where the immune system threatens graft survival.

Recent discoveries of immunologic phenomena at the cellular level have enabled scientists to understand many of the events taking place during an allergic reaction. These findings are being clinically applied at 17 Asthma and Allergic Disease Centers established around the country by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH).

Principles of immunology are also being applied to the clinical problems of organ transplantation. Although surgeons can successfully transplant almost every body tissue and organ, techniques to make the body accept grafts are far from fully developed. Various components of NIH -- but, particularly, NIAID -- are endeavoring to solve this problem through continued support of research which, in the past, has led to many advances in transplantation immunology.

Obligations for programs in Clinical Immunology: Allergy and Organ Transplantation

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health:					
National Institute of Allergy and Infectious Diseases.....	$9,691,000	$10,095,000	$12,017,875	$10,816,088	$11,140,571
National Cancer Institute*	1,809,000	1,538,500	2,958,000	3,300,000	3,600,000
National Eye Institute*	250,000	280,000	310,000	300,000	300,000
National Heart and Lung Institute*..	3,100,000	3,900,000	4,407,000	4,200,000	4,200,000
Division of Research Resources*	3,823,000	3,473,000	2,705,000	2,640,000	2,640,000
Total	$18,673,000	$19,286,500	$22,397,875	$21,256,088	$21,880,571

* Figures are for organ transplantation only.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Allergy

The National Institute of Allergy and Infectious Diseases has estimated that approximately 17 out of every 100 Americans -- or more than 35 million persons -- suffer from one or more major allergic disorders. An allergy is, very simply, reaction to a substance which causes no reaction in most people. Among the most common allergens are foods, pollens, mold spores, drugs, animal danders, insect venoms, and house dust.

In many ways, allergic responses are similar to those which protect us from infectious diseases. In both reactions, substances known as antibodies are usually produced and circulate in the blood. During an infection, these antibodies are protective; they fight and kill the invading microorganism. However, in an allergic reaction, antibodies are produced which sensitize the subject to a substance. With each succeeding exposure to the allergen, more sensitizing antibodies, known as immunoglobulin E (IgE), are produced until eventually the symptoms of allergy develop whenever the allergen is encountered.

Scientists do not understand completely how antibodies cause allergy symptoms. They do know, however, that IgE causes certain sensitized tissue cells, called mast cells, to release chemical mediators. These mediators, in turn, lead to the varied symptoms of allergy -- such as nasal swelling and congestion or bronchial constriction.

Histamine, the first chemical mediator identified, was recovered from sensitized guinea pig lung tissue more than 40 years ago. Since that time, many NIAID grantees such as Dr. K. Frank Austen of Robert B. Brigham Hospital in Boston and Dr. Charles W. Parker of Washington University in St. Louis have played important roles in defining the sequence of biochemical events which occurs in allergic reactions.

Recently, Dr. Austen's research has provided some insight into one control mechanism of the acute allergic reaction -- how an enzyme inactivates the chemical mediator SRS-A (slow-reacting substance of anaphylaxsis, an acute allergic reaction). For many years physicians have recognized that eosinophils, one type of leukocyte or white blood cell, are abundant in the secretions, blood, and affected tissues of allergic people and those with parasitic infections. More recently, it has been shown that these eosinophils contain an enzyme -- arylsulfatase 2B. Dr. Austen's group has now demonstrated that this enzyme inactivates SRS-A, suggesting some control over the allergic reaction. Varying degrees of efficiency of action of this enzyme may account for differences in the severity of allergic reactions. This series of events has not been demonstrated to occur in non-allergic people.

Immunology, the basic study of how the body responds to various foreign materials, such as infectious microorganisms or plant pollens, underlies the field of allergic disease. In recent decades, advances in immunology have given impetus to studies of allergy. One of the most important of these advances was the isolation in 1966 of IgE antibodies by NIAID grantees Drs. Kimishige and Teruko Ishizaka while at the Children's Asthma Research Institute and Hospital in Denver. These scientists are now at Johns Hopkins University.

In 1971, in recognition of expanding knowledge in allergy and immunology, the NIAID initiated its Asthma and Allergic Disease Centers (AADC) program. This program is designed to hasten the translation and application of fundamental knowledge of immunology into improved methods of treating allergic patients. All of the institutions involved had ongoing laboratory research programs in immunology

before becoming Centers. The Center grants permitted them to establish related clinical studies, primarily on an out-patient basis.

There are 17 Centers located throughout the country: National Institute of Allergy and Infectious Diseases, Allergic Diseases Section, Bethesda, Maryland; Scripps Clinic and Research Foundation, LaJolla, California; Johns Hopkins University, Baltimore, Maryland; Robert B. Brigham Hospital, Boston, Massachusetts; University of Michigan, Ann Arbor; Washington University, St. Louis, Missouri; State University of New York, Buffalo; University of Wisconsin, Madison; Creighton University, Omaha, Nebraska; Duke University, Durham, North Carolina; Northwestern University, Chicago, Illinois; Louisiana State University, New Orleans; Mayo Foundation, Rochester, Minnesota; University of California, San Francisco; and National Asthma Center, (formerly CARIH), National Jewish Hospital and Research Center, and the University of Colorado, all of Denver.

In addition to supporting Centers and other research grants in allergy and immunology, NIAID has a small contract program for preparing standardized research materials needed by investigators. Ragweed antiserum (serum containing antibodies to ragweed antigens) and three allergenic components of ragweed (antigens E, K, and Ra3) have been produced and are now undergoing certification. In 1974, work began on producing antisera for human IgE and on the establishment of an allergen certification laboratory. Antibody to human IgE could be used for a promising new laboratory allergy test, the radioallergosorbent technique, or RAST.

AADC Director Dr. Gerald J. Gleich of the Mayo Foundation Graduate School of Medicine in Rochester, Minnesota, is investigating the factors controlling the production of IgE. First, he determined the quantity of IgE antibodies in human blood and then measured and compared the levels of these proteins in the blood of ragweed hay fever patients both before and after the ragweed pollination season. In most cases, the levels of IgE antibody doubled, and in one case it increased six-fold. Interestingly, the ratio of ragweed-specific IgE antibodies to total IgE protein did not change. Both before and after the season, they accounted for approximately 35 per cent of the total. Scientists have long suspected that the severity of allergic diseases is related to the levels of IgE antibody in a patient's blood, and these findings appear to support this theory. Dr. Gleich is now pursuing this subject by evaluating the effect of immunotherapy, or allergy "shots," on IgE levels during the course of a year.

Asthma. Asthma is a noncontagious disease of the large and small bronchial tubes which affects an estimated nine million Americans. Normally, the airways offer little resistance to the flow of air. But, during an asthmatic attack, the mucous lining of the bronchi becomes swollen with fluid, viscous mucus is secreted and blocks the small tubes, and spastic contractions of smooth muscles in the lung area practically close down the passageways of the bronchioli (the extremely fine tubes of the airways). Breathing out becomes increasingly difficult, and the rush of air through the narrowed passageways gives the wheezing sounds that are typical of asthma.

Dr. Robert G. Townley, director of the Center at Creighton University is using the known sensitivity of the bronchial airways to the chemicals methacholine and histamine to study the natural course of bronchial asthma. He found that approximately 85 percent of persons who had asthma up to 20 years ago still demonstrate a marked degree of sensitivity to inhalation of the two study chemicals. Dr. Townley is now attempting to use these tests of airway sensitivity to determine which people, predisposed to allergy, are at high risk of eventually developing asthma. He has already shown that almost one-half of the people with allergic rhinitis have some level of sensitivity to these chemicals, and he has, in fact, accurately predicted the development of asthma in several subjects. The ability to identify persons at high risk of developing asthma may enable physicians to institute preventive measures such as advice concerning occupational and environmental hazards.

Allergic Rhinitis. Better known as hay fever, this form of allergy is commonly caused by inhaled pollens of trees, grasses, or weeds. Airborne mold spores, house dust, and animal danders are also frequent allergens. An estimated 14.6 million Americans are hay fever sufferers.

A common form of therapy for this disease is immunotherapy, or "allergy shots." This treatment method attempts to increase the patient's tolerance for the pollen to which he is allergic. This is accomplished by injecting diluted extracts of the troublesome pollen. The allergist begins with small doses once or twice a week and follows with increasingly larger doses less frequently, as governed by the patient's response. The size of the largest dose is determined by the tolerance of the patient and the therapy's effect on his symptoms. It may take several years for a significant reduction of symptoms to take place.

Dr. Roy Patterson of the Asthma and Allergic Disease Center at Northwestern University is investigating the use of only a part of an allergen in injections. A number of researchers are chemically breaking up substances, such as crude ragweed, to determine which components cause allergies. So far, four fractions of ragweed have been isolated -- antigens E, K, Ra3, and Ra5. Dr. Patterson prepared a polymerized form of antigen E, a principal allergen in ragweed, by chemically linking together identical molecules of the antigen. Clinical studies are now underway using this material in immunotherapy.

If proven effective, use of these materials could mean that fewer injections would be needed. This would result in a considerable savings in time, money, and discomfort on the part of the patient.

Insect Allergy. Stinging insects such as bees, yellow jackets, wasps, hornets, and fire ants, are the cause of dramatic allergic reactions. A single sting of one of these insects in someone sensitive to them can lead to a serious drop in blood pressure, shock, and possibly death. Annually in this country, there are more than 50 reported fatalities from such stings. Undoubtedly many more deaths occur but are diagnosed as heart attacks, stroke, or convulsions.

For many years, physicians have been treating these patients by immunizing them with extracts prepared from the whole insect body. It is difficult to determine when such immunotherapy can be discontinued, and, since this treatment has not always been successful, the allergic person must always have emergency medication nearby in case of a sting.

Of course, exposure is not to the whole insect, but rather, to the venom injected during the sting. Two Asthma and Allergic Disease Centers are involved in identifying the principal allergen in insect venom and evaluating a purified extract. Dr. Philip S. Norman and his associates at Johns Hopkins University have shown that the use of whole bee venom, as opposed to whole-body extracts is significantly more accurate in diagnosing an allergy to stinging insects. In a small number of patients, honeybee venom extract appeared to confer better protection. A treatment study with yellow jacket venom has had similar positive results.

Dr. Carl E. Arbesman and his associates at the State University of New York, Buffalo, have also evaluated the RAST test for use in diagnosing insect sting allergy. Using bee venom and whole body extracts, they showed that the RAST test is very specific, safer than skin tests, and more accurate. It may also prove useful to the practicing physician as a method for determining when to start or stop immunotherapy.

These studies are now continuing, but investigators face the problem of how to obtain sufficient quantities of insect venoms. Large quantities of pure venom are needed for these studies and also for chemical fractionation investigations directed toward isolating the major allergenic components. Venoms from the yellow jacket and bald face hornet are especially difficult to collect. Therefore, researchers such as Dr. Willard Elliott at the State University of New York, Buffalo,

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are investigating new techniques for obtaining these venoms.

Immunodermatology. Allergies affecting the skin may take many different forms, the most common being eczema, urticaria (hives), angioedema (giant swellings of body tissues), and contact dermatitis. The causes, however, may be even more varied. Foods, cosmetics, fabrics, metals, and plant resins are probably the most common.

One AADC Director, Dr. Rebecca H. Buckley of Duke University Medical Center, is studying eczema patients to determine the basic mechanisms leading to the development of allergic diseases. In general, there are two types of immunity: humoral immunity, which depends on antibodies that circulate in the bloodstream and body secretions and that react against foreign materials; and cellular immunity, which utilizes various types of protective cells rather than antibodies. The production of IgE antibodies is part of the humoral immune system, but Dr. Buckley is attempting to determine if cellular immunity also plays a role in allergies.

In studying patients with allergic eczema, the allergy in which the greatest amount of IgE can usually be detected, Dr. Buckley found that cellular immune responses were strikingly depressed and that the degree of depression correlated with the extent and severity of the eczema. These findings support the theory that excessive production of IgE may be associated with a deficient cellular immune function in patients with allergic disorders.

Dr. Allen P. Kaplan, director of the AADC in the NIH Clinical Center, is studying another form of skin allergy, urticaria resulting from exposure to cold. Not only can such allergy to cold result in the raised, itchy lesions of hives, but it can also lead to a precipitous drop in blood pressure, fainting, severe shock, and sometimes death. Some experts believe that some unexplained drownings may actually represent cases of allergy where the cold water caused the swimmers to faint, and then drown.

Dr. Kaplan has shown that cold urticaria results from the release of histamine from body tissues as they begin to warm up after a cold stimulus. Extremely high histamine levels were shown to coincide with episodes of very low blood pressure, the cause of fainting. Dr. Kaplan was also able to identify IgE in the blood of some of these patients. He purified it and is now studying its mechanism of action in cold urticaria.

Systemic vasculitis is a generalized inflammation of the blood vessels which affects both children and adults. The skin lesions it causes are usually clusters of purplish-red spots, resulting from hemorrhages in the skin. In many cases the cause is unknown.

Dr. K. Frank Austen and others at the AADC at Robert B. Brigham Hospital, Boston, have identified a group of patients with chronic urticaria who were found to have an unusual kind of vasculitis. They exhibited classical chronic urticaria accompanied by episodic joint pain and sometimes abdominal pains. This syndrome appears to occur predominantly in females. Since vasculitis is diagnosed by a skin biopsy, these scientists now find biopsy of all patients with urticaria of unknown origin potentially useful and productive.

Hypersensitivity Lung Disease. Pulmonary diseases resulting from occupational and environmental exposure to inhaled fungi, chemicals, and organic dusts are of increasing concern. The Center at Louisiana State University, under the direction of Dr. John Salvaggio, is investigating how the lung defends itself against these substances, especially the immune mechanisms involved.

Hypersensitivity lung disease is also known as hypersensitivity pneumonitis. This immunologic condition causes shortness of breath and weight loss. It often develops in workers who are exposed to organic dusts in their occupations, such as farmers feeding silage to cows or workers in the sugar cane processing industry.

Other important industrial substances suspected of causing hypersensitivity lung disease include beryllium, asbestos, and TDI (toluene diisocyanate, a widely used chemical in the plastics industry). The absenteeism and disability associated with hypersensitivity lung disease affect many different industries and, potentially, large numbers of workers.

The development of an experimental animal model for studying this disease is important, and Dr. Salvaggio's work this past year has made significant progress in this area. Using rabbits, Dr. Salvaggio was able to reproduce the lung damage and certain immune responses of the human disease. His results indicated that the particle-like nature of the mold antigen is an important factor leading to the production of hypersensitivity lung disease. Because the antigen is insoluble and remains a particle, body cells ingest it but cannot dissolve it and diseased areas form, similar to the way a pearl forms in an oyster.

Organ Transplantation

Over the years, NIAID has been instrumental in the development of transplantation immunology. Standard procedures and materials for tissue matching were developed by NIAID contractors and NIAID grantees and intramural scientists continue to work on the problems which, at present, prevent organ transplantation from being a routine part of patient care. For example, new techniques must be found to identify the subtle differences between tissues of organ donors and recipients which may be responsible for the continuing number of rejections by supposedly well-matched patients. New ways to preserve organs must also be developed in order to gain additional time for ideal matching of the donated organ and recipient.

Immunosuppression of the organ recipient -- a technique used to prevent graft rejection -- poses many problems, including drug toxicity. The precise mechanism of action of immunosuppressive drugs must be determined if hazards are to be minimized and therapeutic effects amplified. In addition, methods must be found to monitor the degree of immunosuppression in patients so their increased risk of infectious diseases and cancer can be recognized at the earliest possible moment.

HL-A Antigens. A donated organ is rejected because the recipient's immune defense system "recognizes" it as "foreign matter." This genetic problem would not exist if everyone had an identical twin. For most organ recipients, a brother or sister is the best choice as a donor since there is at least a one in four chance of siblings inheriting identical HL-A antigens from their parents. These antigens are substances found on the surface of certain cells which determine the compatibility of donors and recipients.

Each individual's cells possess four HL-A antigens, two from his mother and two from his father. An individual's HL-A profile is determined through serological (blood) tests with antibodies that recognize each of the known antigens. Acquisition of typing sera for identification of HL-A antigens was the first priority of NIAID's Transplantation and Immunology Branch, established in 1965. This branch is now the leading source of HL-A and H-2 (mouse histocompatibility system) typing reagents throughout the world.

The NIH Serum Bank, located in Bethesda, contains over 280 liters of 1600 different typing sera, which identify the known HL-A antigens. The standardized NIH typing tray contains 68 of the most reliable of these reagents. In FY 1974, over 22,000 trays were delivered to more than 116 U. S. laboratories involved in tissue matching for solid organ and bone marrow transplants. Availability of this tray has enabled scientists throughout the country to have the same basis for typing organs and recipients and, thus, to exchange organs and data.

Transplantation Genetics. Understanding the basic biology, chemistry, and genetics of the immune response is necessary if scientists are going to manipulate man's immunologic functions -- as in organ transplantation -- and solve the problems related to this manipulation.

A large number of genes -- which control several critical functions for the immune system -- have been found in the same region of the chromosome as the genes which control the histocompatibility antigens. In this region, known as the major histocompatibility complex (MHC), is also an important group of genes which control the capacity to make specific immune responses. These immune response genes (Ir) and their products have been the subject of intensive research by NIAID scientists.

Recent studies by Drs. Ethan Shevach, Ira Green, and William Paul have demonstrated that the products of Ir genes play important roles in the recognition of antigens by T lymphocytes (thymus-derived white cells that conduct the cellular immune response). These products, expressed on the cell surfaces, probably exist as a molecular complex with certain types of histocompatibility antigens. Experiments carried out by Dr. Shevach in collaboration with Dr. Alan Rosenthal have demonstrated that MHC genes also play important roles in the cellular interactions between macrophages (scavenger cells) and T lymphocytes vital to the development of the immune response.

These experiments provide insights into the mechanisms by which the immune system functions. They also help explain the increased susceptibility of persons with a certain HL-A type to specific disorders, such as multiple sclerosis and ankylosing spondylitis -- an arthritic-like disease of the spine. The most likely explanation for this susceptibility is that such individuals possess a histocompatibility-linked immune response gene which allows them to make an immune response leading to the disease in question. To control such diseases, it will be necessary to know the chemical nature and biologic function of products of the specific immune response genes.

Immunologically Privileged Sites. Studies involving transplants in immunologically privileged sites -- places in the body where the immune system does not function as expected -- should also provide insights regarding mechanisms of tissue rejection.

The uterus is such a site. Although the fetus is never antigenically identical with the mother, her immune system does not reject and destroy it.

At the University of Texas, Dr. Rupert Billingham, an NIAID grantee, and Dr. Allan Beer, an NIAID contractor, are investigating the immunologic capacities of sperm, fetus, and uterus. They have shown in experimental animals that females, during pregnancy, do develop immunity to their fetuses, despite an inability to harm them. This immunity seems to be biologically important since it helps to determine the size of the placenta, thus indirectly affecting the growth of the fetus. Also subtle differences between individuals, responsible for normal graft rejection, seem to be beneficial in another sense -- they seem to facilitate the implantation of fertilized eggs and their development to term. The fact that genetically alien fertilized eggs are more hospitably treated in a sensitized uterine environment discourages the proposed use of transplantation antigens as a feasible means of conception control.

After birth, maternal antibodies are known to be transferred in the mother's milk to the immunologically naive infant. In man, these proteins are potent sources of harmful allergic reactions, possibly including sudden infant death syndrome.

In studying rats, Drs. Billingham and Beer have found that, in addition to antibodies, appreciable numbers of immunologically competent lymphocytes can be transmitted from a mother's milk to her offspring. In rats suckled by foster mothers, these cells are capable of inducing graft-versus-host disease. Other immunologic reactions of these foster-nursed newborns were altered, probably due to their precocious immunocompetence provided by the transmitted cells.

Immunosuppression. To prevent the rejection of a transplanted organ, scientists try to suppress the body's immune reaction to the graft. This has generally

been accomplished through use of immunosuppressive drugs or antilymphocyte globulin (ALG) -- a serum prepared in animals against the human white cells involved in the immune response. In animals, ALG destroys the white cells, preventing or delaying the development of an immune response. As a result, acceptance of grafts is often prolonged.

However, the effectiveness of this treatment has not been clearly established in humans. National Naval Medical Center scientists, supported by an interagency agreement with NIAID, developed a type of ALG, rabbit antihuman thymus globulin (RAHTG), which they found effective in sub-human primates. This RAHTG is being evaluated in 100 kidney transplant patients at the University of California. The effect of this drug upon the patient's immune response will be determined through special immunologic tests. These tests and the statistical analysis of data are being conducted under an NIAID contract.

If immunosuppressive drugs are to be appropriately used to prevent graft rejection, knowledge of their mechanism of action is essential. Studies on these mechanisms and their effects on the patient's immunologic defenses are being carried out by NIAID scientists. Drs. Anthony S. Fauci and Sheldon M. Wolff have provided a clearer understanding of the specific effects of various cytotoxic -- and, therefore, immunosuppressive -- agents used in immunologically mediated or hypersensitivity diseases. Studies of corticosteroids -- the agents most widely used to prevent graft rejection -- have shown that these drugs affect individual subpopulations of the lymphocytes involved in immunologic reactions.

Kidney Transplants. Every year, an estimated 8,000 new patients, in addition to the thousands of patients still waiting from previous years, could be helped by kidney transplants. In 1974, only 3,600 actually received new organs. The majority of these came from cadavers -- people killed in accidents or who died from diseases that would not affect their kidneys. Unfortunately, most of these transplants could not be perfectly matched to the recipients.

While matched HL-A antigens appear to be very important in transplants from living related donors, their significance in cadaver transplants is a matter of debate.

To shed light on this problem, NIAID has initiated a contract-supported Kidney Transplant Histocompatibility Study. Data are being collected and statistically analyzed on approximately 3,000 kidney transplants performed during 1974-1976 in 8 regional centers, involving 37 hospitals. The study will include 2 years of post-transplant follow-up.

Significant contributions to the understanding of human kidney disease before, during, and after a transplant have been made by Dr. Frank Dixon at Scripps Clinic and Research Foundation at La Jolla, California. Under an NIAID contract, Dr. Dixon has examined kidney tissue and blood from nearly 3,400 patients during the past six years, in an effort to determine the mechanisms responsible for the failure of a kidney transplant -- recurrence of the original disease, rejection of the "foreign" organ, or other immunologic processes.

In Dr. Dixon's studies on human glomerulonephritis -- a disease involving tufts of blood vessels in the kidney -- he found several years ago that kidney failure was induced by deposits of protein on one type of kidney membrane. Dr. Dixon has now found evidence of similar deposits of antibody on another type of kidney membrane -- TBM or tubular basement membrane. This latest finding could have important implications for renal transplants, since it indicates the presence of TBM antigens and a patient lacking the TBM antigen could be expected to develop antibodies against a transplanted TBM-positive kidney.

A serious problem in kidney transplants is maintaining the viability of the kidney from the time it is removed from the donor until it is placed in the recipient. Dr. Richard Varco, an NIAID grantee at the University of Minnesota, has

found a method to predict organ viability and function before the kidney is transplanted.

His method involves the measurement of ATP -- adenosine triphosphate -- which is the principal high energy molecule within the kidney cell. Dr. Varco and his associates found a rapid decay of ATP levels in kidneys removed from adult mongrel dogs. However, these levels of ATP could be restored by placing the kidneys on a perfusion machine specifically designed to keep kidneys functioning outside the body for as long as 24 hours.

Kidneys which were reimplanted in the same donor dogs after this treatment functioned well if their ATP levels were greater than 60 percent of the control levels. Those kidneys with less than 60 percent failed, and the dogs died within 10 days. Clinical application of this procedure could thus determine the suitability of a kidney for transplantation.

Skin Transplants. The use of skin grafts by NIAID grantees as Massachusetts General Hospital has achieved significant success in the treatment of severely burned children for whom conventional treatment offered no chance of survival. Dr. Paul Russell and his colleagues remove the burned skin and resurface the areas with grafts of skin from the patient's HL-A matched family member. Survival of the graft is achieved through careful immunosuppression, utilizing knowledge gained through kidney transplants.

ALG -- sera prepared against human white cells -- was used to suppress skin graft rejection in an 8-year-old girl who was burned over 85 percent of her body. After removal of the burned skin, she received skin grafts from her father. The immunosuppression continued for 25 days, during which she received grafts of her own skin on progressively greater proportions of her previously burned areas. When the immunosuppression stopped, all of her father's skin was rejected, but 60 percent of her body by that time was covered with grafts of her own skin. She has recovered completely.

Immunologic Reconstitution. Bone marrow transplants have been shown to be a promising treatment for a number of diseases, including leukemia and aplastic anemia -- the latter a disorder in which the bone marrow fails to produce blood cells. However, transplantation of competent bone marrow cells creates not the rejection phenomenon, but a new problem of graft-versus-host disease (GVH). In GVH, the transferred cells reject and destroy the tissues of host or recipient. To avoid this serious development, bone marrow transplants need to be well matched. Under an NIAID contract, scientists at the University of Washington -- the world's leading bone marrow transplant center -- are evaluating the current typing procedures in this field.

Supported by both NIAID and the National Cancer Institute (NCI), investigators at the University of Washington have carried out extensive marrow transplant studies in dogs, resulting in successful long-term transplants, thus paving the way for similar long-term transplants in an evergrowing number of patients.

In the dog, Dr. E. Donnall Thomas and his coworkers have unravelled the complicated immunologic mechanisms involved in making the cells of the marrow graft donor and recipient tolerant to each other. Encouraged by results of these studies, the scientists have now performed more than 175 human marrow transplants on patients with leukemia or aplastic anemia who had already experienced the maximum possible benefit from conventional therapy. These patients were thought to be within days or weeks of death.

The scientists have found that a bone marrow transplant from a normal identical twin, in combination with chemotherapy, total body irradiation, and immunotherapy, appears to provide a leukemic patient with a good chance for a normal adult life. However, over the years, only 28 of Dr. Thomas' patients have been fortunate enough to have an identical twin to serve as a marrow donor. Nine of

these 28 patients are alive, free of their disease, and living normal lives without any treatment. The longest survivor of this group is at 4 1/2 years.

The remaining transplants at Seattle have been carried out using a brother or sister who is matched as closely as possible with the patient in regard to the major tissue antigens. In 48 patients with aplastic anemia given such transplants, 25 are still alive up to 3 1/2 years later.

In other studies, NIAID intramural researchers investigated a rare, inherited, blood disease in grey collie dogs, similar to a serious blood disease in man, called cyclic neutropenia. This disease is characterized by a periodic precipitous drop in the level of circulating white blood cells that protect the body against infection. During these drops in white blood cell levels, both humans and collies are very susceptible to serious infection. Scientists believe that understanding these human and canine diseases will lead to a better understanding of leukemia and aplastic anemia -- more common fatal diseases in which the white cells play a role.

It is thought that cyclic neutropenia is due to some type of defect in the bone marrow cells which causes the dogs (and humans) periodically to stop producing cells. All previous attempts to stop this cycling in dogs had failed. Therefore, NIAID and NCI investigators transplanted bone marrow cells from a normal histocompatible collie to a grey collie.

After the transplant, the grey collie had no more periods of neutropenia. Chronic inflammation cleared, although she did experience a mild attack of graft-versus-host disease. The dog recovered completely and lived 3 more months with normal production of white cells, dying from causes unrelated to the transplant or the neutropenia.

Defects in an individual's cell-mediated immune response can also result in an unusual susceptibility to certain chronic infectious diseases. In chronic mucocutaneous candidiasis -- a disfiguring infection caused by a fungus -- patients are unable to respond appropriately to the fungus antigen. Using transfer factor -- a substance extracted from immune white cells -- Dr. Charles Kirkpatrick of NIAID has been able to correct this problem and prevent the recurrence. Patients who did not respond were found to lack T cells. One non-responder received a thymus transplant, subsequently produced T cells, and then responded to transfer factor therapy.

Division of Research Resources

Currently there are 82 active projects involving organ transplantation being conducted in the Division of Research Resources' General Clinical Research Centers. One area of organ transplantation research with immense potential involves immunosuppressive agents, a number of which have been developed and evaluated at the Centers. The most promising agent is a serum antilymphocyte globulin (ALG). ALG differs from other immunosuppressive agents in that it is a biologic material and is essentially nontoxic. Since it acts selectively against lymphocytes, it may prove to be the safest and most effective agent available. Its development and evaluation is an excellent example of basic research leading to clinical trial and then to therapeutic acceptance and benefit.

National Eye Institute

Several thousand cornea transplants are performed annually in the U.S. to restore vision lost through disease or injury to the cornea -- the transparent, protective layer which covers the front of the eye. However, 10 to 15 percent of these transplants fail for immunologic reasons. Investigation of these factors is being supported by the National Eye Institute (NEI).

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Preliminary studies by an NEI grantee indicate that, as in kidney recipients, sensitization of a cornea recipient to HL-A antigens in the form of HL-A antibodies, increases the chances of graft rejection. As a result, prospective cornea recipients are being screened for the presence of these antibodies. To further increase the graft's chance of survival, both donor and recipients are being HL-A matched.

NEI is also supporting research to improve methods for storing corneas until they are transplanted, since present techniques have severe limitations. One method — refrigeration -- requires that corneas be transplanted within 48 hours of the donor's death. This storage time can be lengthened to several months if another method -- cryopreservation -- is used. However, this technique, in which corneas are frozen at extremely cold temperatures, requires prompt handling (within 6 hours of donor's death), special equipment, and expert technicians.

Rabbit corneas have been successfully transplanted by one NEI grantee after storage for one week in a special chamber that is readily available. Similarly stored human corneas appear to survive well when examined by electron microscopy. In the standard moist chamber, cornea survival was improved by using a special tissue culture solution.

National Heart and Lung Institute

Transplantation Biology. The recipient of an organ or tissue transplant frequently requires transfusion of whole blood or blood products before, during, or after the transplantation procedure. But transfusions also introduce histocompatibility antigens (HL-A) that may sensitize the patient and threaten survival of the transplant.

Current NHLI-supported studies are pursuing effective means of removing HL-A antigens from blood and blood products. Freezing blood appears to be one method of removing these antigens. Red cells stand up well to conventional freezing and thawing techniques, but other cellular components of blood, such as white cells and platelets, do not. Moreover, present freezing and thawing techniques are relatively cumbersome and costly, and many hospitals and blood banks lack adequate freezing facilities. These factors limit the utility of this approach.

Another approach employs a double centrifugation technique to remove white cells and platelets (which appear to carry most of the HL-A antigens of whole blood) prior to transfusion. This technique is relatively simple and holds promise for transfusion therapy in those transplantation candidates whose chief blood deficiency is anemia.

Other NHLI-supported research is concerned with the development of devices and techniques for the preservation of organs and tissues prior to transplantation. Such developments would make possible a more equitable system of organ procurement and distribution on a regional or national basis. Also germane to this endeavor is work now in progress with support from NHLI, other Institutes of NIH, and other agencies toward the establishment of a nationwide blood system and regional blood centers. Such centers may well be joined by regional transplantation centers to be engaged in organ acquisition, and preservation, in tissue typing and other immunological procedures to secure the best possible match of transplant to potential recipient, and in distributing suitable transplants to sites of need as these arise.

Heart Transplantation. Heart transplantation is riskier than kidney transplantation and the results far less predictable. But substantial progress continues to be made in a few centers with adequate facilities, staff, and experience to deal with the immunological problems that nearly invariably develop during the post-operative period.

The group with the most intensive clinical experience and the most impressive

results has been that headed by Dr. Norman Shumway at Stanford University. As of August, 1974, this team had performed 73 heart transplants. Currently, one-year survival is 50 percent (though among all patients in the series it is 44 percent); and the group believes that a one-year survival rate of 65 percent is likely to be achieved among subsequent patients. The survival rate for two years has been 39 percent; for three years, it has been 24 percent; and for four and five years, 20 percent.

It is noteworthy that the chief cause of death among transplant recipients in this series has been infection (26 deaths), followed by graft rejection (10 deaths), and coronary atherosclerosis in the transplanted heart (6 deaths). For a time it appeared that coronary atherosclerosis, which developed rapidly in most of the early transplants, might be the most critical factor limiting long-term survival. But the scientists report that this problem has been largely eliminated through long-term administration of oral anticoagulants, dipyridamole (an agent that inhibits the aggregation of blood platelets), and diets to hold down blood levels of cholesterol and other lipids.

The most critical period is the first two months after transplantation, when acute rejection episodes are very likely to occur. It is extremely important to detect these episodes early, treat them vigorously, and then discontinue heroic immunosuppressive therapy promptly when the episode ends.

Earliest detection of acute rejection episodes is provided by a blood test called the modified reactive leukocyte blastogenesis (MLRB) assay. This test involves culturing the patient's white blood cells in a medium containing radioactively labeled thymidine, a building block in the synthesis of DNA -- deoxyribonucleic acid, which contains genetic information for the cell. The mobilization of the patient's immune mechanisms, which precedes the assault on the transplant, is heralded by rapid multiplication of white blood cells, which incorporate the labeled thymidine in their DNA. An increase in the number of labeled white cells signals the onset of the rejection episode.

The episode is also monitored by the electrocardiogram, clinical tests, and serial heart-tissue biopsies, which can be obtained simply and safely with a catheter-mounted device threaded into the heart through the jugular vein.

The scientists believe that clinical studies on heart transplantation should continue since, in skilled hands, it provides optimistic prospects for several years of near-normal living to patients who otherwise stand no chance of surviving beyond a few days, weeks, or months.

Lung Transplantation. From 1963 through December 1974, 35 lung transplants were attempted in patients moribund from far-advanced lung disease. The longest survivor lasted 10 months. Most others succumbed within 10 days, many within hours of operation, and usually because the transplanted lung or lobe failed to assume normal function after transplantation.

At present, there seems little clinical justification for attempting lung transplants in humans. But the especially formidable problems posed by lung transplantation should continue to be studied in the laboratory and in experimental animals, as they are with NHLI research support.

National Cancer Institute

Study of patients with aplastic anemia has permitted an indepth investigation into the clinical management of cancer patients who develop "marrow failure" as a result of conventional therapies. Bone marrow transplants in patients with leukemia have allowed the administration of otherwise lethal doses of drugs and radiation, producing disappearance of symptoms of leukemia in about one-fourth of the patients.

Following marrow transplantation, patients are very susceptible to infections. Laminar air-flow environments that isolate the patient from disease-causing micro-organisms and filter his air supply are being used at the National Cancer Institute and the University of Washington in the postoperative supportive care of patients receiving marrow. These studies will indicate whether such environments can lessen the number of severe infections in transplant recipients.

NCI also shares in the funding of the American College of Surgeons-National Institutes of Health Organ Transplant Registry. Data on marrow transplant recipients from 27 centers around the world are filed at the Medical College of Wisconsin. This information is a valuable resource for evaluating the transplant procedure.

In addition, the registry is used to monitor the occurrence of cancer in patients who receive solid organ transplants. These patients were given drugs that suppress their immune system, to prevent rejection of their transplants. A recent report by NCI epidemiologists showed that the incidence of one form of cancer -- lymphoma -- in kidney transplant recipients is 35 times that normally expected in the general population. This finding suggests that a healthy immune system may be important in preventing cancer.

COOLEY'S ANEMIA

The study of the processes and functions of blood cells and other constituents is essential to provide insight into the genetic basis of inherited blood disorders such as Cooley's anemia. It is estimated that there are more than 1,000,000 persons in the United States who suffer from disabling or killing disorders of the blood, including the anemias and bleeding disorders.

A recent national survey of physicians showed that at least 2,400 patients with Cooley's anemia are being maintained with the aid of chronic transfusion therapy. Worldwide, the problem is of greater scope with the thalassemias being the most common inherited single gene defect. On Cyprus, for example, 1 in 200 inhabitants has Cooley's anemia, and 15 percent of the population carries the trait. Where blood transfusion is not readily available, life expectancy for those afflicted seldom exceeds 2 to 4 years.

Obligations for Programs in Cooley's Anemia

	1973	1974	1975 Estimate	1976 Estimate
National Institutes of Health:				
National Institute of Arthritis, Metabolism, & Digestive Diseases				
Cooley's anemia	$ 992,000	$1,224,000*	$1,158,000	$1,208,000
National Heart and Lung Institute:				
Cooley's anemia	$1,121,000	$1,206,000	$1,325,000	$1,325,000
Total	$2,113,000	$2,430,000	$2,483,000	$2,533,000

National Institutes of Health
National Institute of Arthritis, Metabolism, and Digestive Diseases

A steady advance has been made in our knowledge of Cooley's anemia, (also known as Thalassemia Major and Minor, Mediterranean anemia, Hereditary Leptocytosis, and Familial Microcytic anemia) much of it during the past decade. Diagnostic techniques in the blood diseases have become more precise, and prompt and accurate diagnosis is frequently the key to initiating treatment that extends life. Institute-supported research has contributed much to knowledge of the molecular structure of hemoglobin, the key substance in red blood cells which carries oxygen from lungs to tissues, and of the disordered sequence of amino acid building blocks in abnormal hemoglobins.

Through research in its Bethesda laboratories and clinics, and through numerous grants to scientists at research centers across the country, the National Institute of Arthritis, Metabolism, and Digestive diseases (NIAMDD) is investigating many blood disorders, including Cooley's anemia. The National Heart and Lung Institute (NHLI) shares the responsibility for Cooley's anemia research with NIAMDD. Blood is such a

* Includes $119,000 in 1974 from restoration of 1973 impounded funds.

complex substance that any new discovery about it will open possibilities of biomedical investigation in related fields as well. For example, the development of a cell-free system for studying hemoglobin synthesis not only provides new information that may be applicable to the genetic control of this process, but can also serve as a prototype for the synthesis of other proteins in other tissues. This past year investigations have contributed many important research findings.

National Cooley's Anemia Control Act

New initiatives and investigations are forthcoming in the area of Cooley's anemia following passage of the National Cooley's Anemia Control Act, which provides for expanded programs of research, diagnosis, prevention and treatment of this disorder. The main responsibility for conducting research in Cooley's anemia rests with the NIAMDD. Under the provisions of the National Heart, Blood Vessel, Lung and Blood Act of 1972, however, a comprehensive national plan for the future research needs in Cooley's anemia will be included in the NHLI's report required under that Act.

Cooley's Anemia: The Disease

Cooley's anemia is an inherited blood disorder which occurs primarily in persons of Mediterranean ancestry. In the United States most of the victims are of Italian, Greek, Turkish, Southern French or North African descent, although the disease is not limited to these groups.

As in many genetic blood disorders, those who inherit the trait for the disease from only one parent will become "carriers" (who can pass on the trait to their own offspring) and are usually free of symptoms; those who inherit the gene from both parents have the overt disease. This severe form of the disease occurs, on the average, in one fourth of the children of parents who both carry the trait. Cooley's anemia is characterized by the production of abnormally thin red blood cells with abnormal mechanical fragility and by a profound anemia which appears soon after birth; severe effects include enlargement of its spleen and liver and grossly active bone marrow that may produce thickening of facial bones. The anemia is due to the inability of the bone marrow to synthesize a complete hemoglobin protein. This results in abnormal red cells that are then removed from the circulation by the spleen, reducing the overall number of red blood cells available for transport of oxygen from the lung to all body tissues.

No cure is known, and the only effective treatment is repeated administration of blood by transfusions, usually once a month but sometimes more frequently, to alleviate the constantly recurring anemia. A serious complication is a progressive overload of iron in the body resulting from frequent transfusions. Carriers generally enjoy normal health and life span. The prevalence is not really known but the best available estimate is that about 200,000 persons in this country carry the trait.

Diagnosis is relatively straightforward in those who have clinical disease, but definitive diagnosis in those who only carry the trait is much more difficult and requires relatively sophisticated hematologic tests.

Inter-Institute Coordinating Committee

The National Institutes of Health has formed an Inter-Institute Committee on Cooley's anemia in order to assure that the research efforts related to the disease are coordinated into an effective total effort.

A top priority program in relation to the Cooley's Anemia Control Act is the search for a more effective chelating agent for removal of the undesirable iron stores resulting from repeated blood transfusions to patients. Several research contracts for development of such an agent have been let and funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases during Fiscal Year 1974.

The contractors, together with other experts from across the country, attended a workshop at NIH in September, 1974, to coordinate their activities. The investigators foresee the development of a safe and effective chelating agent.

Iron Chelating Agent

Clinical trials will attempt to determine the usefulness of drugs designed to increase excretion of excess iron from the body. Known iron chelators do increase iron excretion, but their value in improving health and preventing the complications of iron overload has not been determined. Efforts are under way to evaluate a wide range of compounds for safety and effectiveness in preventing damage from accumulations of this element. Promising compounds of microbial origin, as well as those synthesized in chemical laboratories, will be developed and evaluated first in animals for biological safety and effectiveness.

Over the next several months physicians from many cities will cooperate in designing trials. Patients with Cooley's anemia will be asked to participate in the studies.

Promising Animal Studies

The initiation of a pilot clinical trial to evaluate the compound 2,3-dihydroxybenzoic acid (2,3-DHB) is now underway by an NIAMDD grantee, Dr. Anthony Cerami, and associates, at the Rockefeller University in New York. They have reported promising animal studies with the compound which will now be evaluated in the treatment of patients with iron-overload resulting from transfusions. The compound, which can be administered orally, removes iron from an overloaded rat without affecting the excretion of other needed trace metals. Adverse toxic effects have not been observed to date in the animals. These studies, to be conducted in selected patients, are expected to establish whether this drug has a feasible therapeutic role in iron-overload in Cooley's anemia.

Using DF in Iron Removal

At the present time, only desferrioxamine (DF) is available generally in the U.S. for removing excess iron. The drawbacks to its use are two:

1) removal of iron by DF is demonstrated only after the body's iron stores have become saturated and the pathological accumulation has begun, which means it may not be effective in preventing iron overload, and, 2) it must be given daily by deep intramuscular injection. The NHIL will test DF in national cooperative clinical trials to determine if its use will materially benefit patients by preventing or slowing the pathological effects of excess iron.

Cooperative Clinical Trial

The National Heart and Lung Institute plans to conduct another study of importance in the Cooley's anemia program. This is a cooperative clinical trial to study transfusion therapy for children with Cooley's anemia. While frequent blood transfusions result in better growth and less liver, spleen and bone abnormalities, the long-term effects of additional iron accumulation due to the increased transfusions are a source of concern. Therefore, careful study is essential to determine the optimal number of blood transfusions.

Cooley's Anemia Screening Test

Now underway at the National Heart and Lung Institute is a pilot program of screening for thalassemia trait and counseling for those affected with the condition. The principal question to be answered is whether or not a mass screening program for Cooley's anemia should be considered for the country. A large scale screening program would require development of a simple, inexpensive screening test. Such a test is not available at present and has defied development thus far. The NHLI is also field testing a procedure which identifies possible both sickle cell anemia and Cooley's anemia carriers, using micro-chromatography techniques.

The Health Services Administration (HSA) of the Public Health Service also plans to fund a small service-oriented screening, counseling and education program in cooperation with the Cooley's Anemia Foundation. The HSA effort and the NIH pilot programs in screening will be coordinated to insure maximum benefit from the knowledge gained. The Health Services Administration plans to undertake, within available funds, a Genetic Blood Disorders program in accord with requirements of Title II of the PHS Act. The program would include both Part A, Sickle Cell Anemia, and Part B, Cooley's Anemia.

Synthesis of Hemoglobin

Research conducted at the National Institutes of Health on Cooley's anemia is carried out in the Molecular Hematology Branch of the National Heart and Lung Institute (NHLI). This program is exclusively involved in clinical and laboratory study of hereditary anemias with primary interest in Cooley's anemia. Any patient with Cooley's anemia, upon referral of his physician and acceptance into the ongoing study, can receive care as part of this program. The Branch also carries out fundamental studies on the underlying defect in Cooley's anemia. NHLI scientists

have synthesized hemoglobin in a cell-free system using components isolated from human red blood cells. These studies have shown that the inherited defect in Cooley's anemia is carried by the genetic molecule messenger RNA and that the cellular defect of the thalassemic cell can be reproduced in a normal cell-free system by the addition of messenger RNA from diseased cells. Studies from several laboratories supported by NIH have now shown that the molecular defect in Cooley's anemia is a deficiency in the amount of normal messenger RNA. Intensive efforts are now being made to develop more effective treatment programs based on this new knowledge.

Outlook

Cooley's anemia is an integral subject of research conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Heart and Lung Institute. The number of Americans afflicted with the disabling and killing disorders of blood, including the anemias, is sufficient to justify the effort. Among the Institutes' research goals is an attack on Cooley's anemia which includes among its goals improved diagnosis, improved methods of detecting carriers of the disease and specific therapy. New research should yield maximal benefits in the number of lives saved today and the deaths prevented in years to come.

CYSTIC FIBROSIS

Although much still remains to be learned about cystic fibrosis (CF), the clinical picture of this inherited metabolic disorder is brighter now than in years past. The exact nature of the basic chemical defect in CF still eludes investigators, but great strides have been made in alleviating the complications of the disease. Striking one in every 1,500 infants, cystic fibrosis is characterized by malfunctioning exocrine glands that secrete abnormal fluid to internal and external body surfaces, particularly to the gastrointestinal and respiratory mucosal linings and the skin.

The Department of Health, Education, and Welfare's research activities in cystic fibrosis are centered in the National Institute of Arthritis, Metabolism, and Digestave Diseases (NIAMDD), a component of the National Institutes of Health in Bethesda, Maryland. Research conducted and supported by NIAMDD is aimed specifically at defining the physiologic effects of the clinical manifestations, at determining the biochemical aberrations associated with the disease and at developing improved methods of prompt diagnosis, more effective treatment, and hopefully, eventual prevention of this disease.

In addition to investigations carried out at the National Institutes of Health laboratories and clinics in Bethesda, the NIAMDD supports many cystic fibrosis research projects at medical centers and institutions across the country through the research grant mechanism. This combined effort has opened up promising new avenues which will lead ultimately to the precise definition of the molecular defect in this metabolic disorder.

Obligations for Programs in Cystic Fibrosis

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, and Digestive Diseases.	$2,777,000	$2,525,000	$2,829,000	$2,367,000	$2,417,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Cystic fibrosis (CF), an inherited metabolic disorder of exocrine secretion, results in three principal clinical problems. The first is the production of sweat with a high salt content. Because of this defect, patients are unable to conserve salt and are therefore at risk of developing profound dehydration or heat exhaustion in the summer, either of which may be fatal.

The second is that in CF the mucus-secreting glands of the body fail to secrete normal, clear, free-flowing fluid. Instead, they produce abnormally thick, viscous mucus which tends to obstruct the ducts or openings of these glands. When the mucus accumulates in the ducts of the pancreas, it interferes with the ability of this gland to supply digestive enzymes to the intestinal tract, thus leading to poor digestion of food and to malabsorption of a number of essential nutrients. Depending on the severity of this complication, the patient may suffer from general underdevelopment, poor musculature, and retarded bone growth.

The third and most serious complication is the development of progessive, chronic lung disease. Thick mucus obstructs the smaller air passages in the lung, causing labored breathing and chronic cough. In time, bacteria multiply in the accumulated secretions, predisposing the child to chronic bronchitis or pneumonia - a leading cause of death in these patients. The lung changes may also restrict pulmonary blood flow, leading to increased blood pressure in the lung and to consequent chronic heart strain and eventual heart failure.

Current Research Status

Many Institute-supported research projects in CF are related to applications of existing medical knowledge to improved treatment, while other more basic studies involve the search for a specific biochemical defect or genetic abnormality responsible for the disease. Some projects have implications for improving tests for early diagnosis (or developing new ones), for elucidating the specific mechanism of exocrine gland dysfunctions, and for determining the nature of the molecular defect in cell components.

A prime factor in the management of this disease is to establish a correct and early diagnosis prior to the development of irreversible pulmonary complications. The most widely used diagnostic test, based upon an abnormally high concentration of salt in sweat, illustrates one of the manifestations of exocrine gland dysfunction. A number of research projects are concerned with secretory mechanisms, including those of the sweat glands, salivary glands, and those of the respiratory and gastrointestinal systems.

A disease of many disguises, CF offers only enigmatic clues to the disorder's basic mechanism. Promising findings in fundamental research and innovative methods of diagnosis and treatment, however, have opened up new avenues for investigation, resulting in a somewhat more optimistic outlook for patients.

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Respiratory Complications

The key to prolonged survival for most cystic fibrosis patients is control of respiratory complications. Chronic pulmonary disease is responsible for death in 90 percent of the cases. Vital respiratory function is the subject of a number of Institute-supported research projects. These include studies concerningpulmonary ventilation, certain complicating, secondary respiratory disorders, cilia of the respiratory mucosa and ciliary movement, and bronchi and bronchial mucus in CF.

Seeking more effective medication for the lower respiratory tract, investigators are evaluating aerosol inhalation therapy. This type of treatment permits small particles of drugs essential for breaking up mucus to penetrate to the lower reaches of the lungs where the air passages are smaller but the surface area is greater.

In addition, research on antibiotics is continuing. A number of safe and effective drugs are in use; resistant strains of micro-organisms, however, which tend to establish themselves in the lungs of patients with CF, particularly pseudomonas and staphylococcus, pose problems in long-term antibiotic therapy. Investigations are underway to evaluate a vaccine against pseudomonas infection as well as the long-term effectiveness of a semi-synthetic penicillin, carbenicillin. Institute investigators have also demonstrated the effectiveness of gentamicin against drug-resistant strains of these two organisms.

Recent research by Institute grantee Dr. LeRoy Matthews and associate Dr. Bernard Boxerbaum has provided one explanation for CF victims' inability to fight off pseudomonas bacteria in the lungs. Studies at University Hospitals of Cleveland have pinpointed a factor in the blood serum of cystic fibrosis patients which appears to inhibit the lungs' defense mechanisms in resisting pseudomonas. The serum, however, has little or no effect on the defensive activity of the lungs against other bacteria.

In CF, the tracheal-bronchial passageways become blocked with mucus, providing a breeding ground for trapped bacteria and other inhaled particles. For unknown reasons, infections in the early stages of cystic fibrosis are almost always caused by staphylococci. As the disease progresses, susceptibility changes primarily to pseudomonas.

The investigators focused on the action of the alveolar macrophages, cells which comprise one of the primary defense mechanisms of the lungs. Rabbit macrophages, when combined with normal blood serum and staphylococcus, and later pseudomonas organisms, killed both forms of bacteria. In CF serum, however, the alveolar macrophages promptly destroyed staphylococci but were significantly less effective against pseudomonas bacteria.

The researchers concluded that childhood treatment of early stage staphylococcal infections with antibiotics may upset the natural defense balance and thereby provide a medium more susceptible to later pseudomonas growth. The studies also revealed that while CF patients may be able to combat successfully pseudomonas bacteria elsewhere in their systems, the lungs are the exception, where macrophages are rendered ineffective. These findings emphasize the importance of continued research on antibiotic therapy, particularly for infections of drug-resistant bacteria.

Pseudomonas Vaccine

Many CF patients (approximately 80 percent) evidence chronic pulmonary colonization with pseudomonas, an organism notoriously resistant to most antibiotics. Recent research by NIAMDD investigator Dr. R. Wood and associates Drs. H. Reynolds and J. Pennington of the National Institute of Allergy and Infectious Diseases measured antibody responses to infection with pseudomonas and to immunization with a vaccine prepared against the species.

Prior to and following administration of vaccine by a series of injections or intranasal spray, antibody levels of CF patients were measured in serum and bronchial secretions. The results indicate that pseudomonas vaccine is well tolerated by both parenteral and intranasal routes, with antibody levels rising significantly following injection. Complete evaluation of nasal administration is underway.

In the group of patients studied, however, no objective improvement in pulmonary function or clinical status was noted, nor was pseudomonas eradicated from any patient's sputum. The investigators concluded that although good antibody responses can be achieved without serious side effects, there is no significant benefit to patients in whom pseudomonas colonization is already well established.

Emphasis is now on the intranasal route of immunization in patients as yet free from pseudomonas. Should the vaccine spray stimulate production of local antibody response in the respiratory tract, an effective immunization program could be established to curb the incidence of new pseudomonas colonizations.

Fiberoptic Bronchoscopy

The development of transnasal fiberoptic bronchoscopy is having a profound effect on pulmonary medicine. The flexible bronchoscope, inserted through the nasal passages down to the bronchial airways, permits bedside and clinic examinations with minimal risk or discomfort.

Dr. Robert E. Wood (NIAMDD) has successfully localized bleeding sites, removed mucus plugs, and obtained secretions for culture and other studies in pediatric patients, with minimal complications. Evaluation of bronchial irrigation to unclog mucus-filled passageways in cystic fibrosis patients is now in progress. The researcher believes transnasal fiberoptic bronchoscopy to be a reliable tool for the diagnosis and management of many pediatric pulmonary disorders.

Mucociliary Transport in Cystic Fibrosis

One such application of the new bronchoscopic technique is observation of the rate of mucus mobility (the normal sweeping motion of the hair-like cilia which line the respiratory airways) and mucus clearance in the bronchial passageways. Chronic obstructive lung disease, one of the most hazardous complications of CF, results from an extremely low rate of mucociliary clearance in these passages.

To measure the rate of airway clearance in adult CF patients, teflon discs were blown onto the tracheal mucosa, and their motion filmed. The findings by NIAMDD investigators Drs. Robert E. Wood, Paul di Sant'Agnese, Philip M. Farrell and associate researchers Judith Hirsch and Adam Warner of the Mt. Sinai Medical Center in Miami indicate that the average rate of tracheal mucus velocity in CF patients is approximately 15 percent of that recorded in healthy persons.

In an effort to improve this rate, patients received a single injection of terbutaline, a bronchodilator which increases expiratory flow rate, with disc movements measured again 15 minutes later. The average mucus velocity doubled in the CF group to one-third that of the normal controls, the first demonstration of pharmacological increases in mucociliary clearance in cystic fibrosis. The investigators believe that further increases may be possible by different drugs, routes of administration, or drug combinations. These observations hold promise in the management of chronic obstructive lung disease, the key to prolonged survival.

Vigorous Therapy Lengthens CF Survivial

Many physicians feel that the prognosis in CF is essentially hopeless, and therefore do not pursue therapy aggressively. To the contrary, a recent epidemiological survey conducted by Dr. Paul di Sant'Agnese and associates of the National Institute of Arthritis, Metabolism and Digestive Diseases indicates that vigorous treatment does increase longevity significantly.

Data were obtained from the National Center for Health Statistics and the National Cystic Fibrosis Foundation on the number of deaths in various age group from 1960 through 1970. Comparison of mortality experience in patients followed in specialized Cystic Fibrosis Centers with patients not treated in such institutions suggests strongly that intensive care results in greatly prolonged survival with an average age at death about ten years beyond that of patients treated outside the Centers.

The study concludes that patients newly diagnosed with cystic fibrosis should be promptly referred to specialized multidisciplinary treatment centers for maximal survival.

Growth and Nutrition in CF Adolescents and Young Adults

Pancreatic deficiency in providing digestive enzymes characterizes approximately 80 percent of cystic fibrosis patients. As a result, much of the daily diet passes through the body undigested, taking with it nutrients needed for adequate growth and development. In very young patients, marked clinical improvement has been noted after initiation of dietary management (reducing fatty food intake) and the addition of pancreatic enzyme supplements. In older patients, however, intolerance to fatty food is less prominent and the state of nutrition is better than that of the younger age group, despite continued loss of fecal fat and nitrogen.

A recent study of fat and nitrogen loss has shown that for the adolescent and young adult cystic fibrosis patient, dietary restrictions and pancreatic supplements have little or no demonstrable effect.

The research by Drs. A. Lapey, J. Kattwinkel, P. di Sant'Agnese and L. Laster, NIAMDD investigators, represents the first comprehensive study of malabsorption in older patients with CF and pancreatic deficiency. The study was designed to evaluate the current clinical status, state of nutrition, and growth achieved in relation to the degree of nutrient loss and adequacy of previous dietary treatment as gauged by the age at diagnosis.

The findings showed that fecal fat and nitrogen loss, frequently massive and widely varied in degree, were present in all study patients regardless of symptoms, state of nutrition, or growth. In fact, many of the patients with better nutrition and prognostic scores had been diagnosed late in life and presumably had not received optimal treatment.

The investigators concluded that these factors did not correlate with the amount of fecal fat and nitrogen loss, adherence to dietary regimen, or adequacy of previous treatment. Rather, the degree of growth failure as well as the state of nutrition was more closely correlated with the degree of severity of pulmonary disease. While pancreatic replacement therapy does improve fecal fat and nitrogen loss somewhat in older CF patients, little dietary restriction is needed, allowing patients to regulate food selection on the basis of symptoms.

Vitamin E Deficiency in Man

The functions of vitamin E in man, at the molecular level, are still unknown, despite the fact that the biological manifestations of vitamin E deficiency are more apparent in various animal species than any other nutrient. Man, however, has not been shown conclusively to develop these symptoms of E deficiency.

Tocopherol (vitamin E) deficiency rarely occurs in normal populations of developed countries. Recent studies, however, by NIAMDD investigators Drs. Philip Farrell, John Bieri, Paul di Sant'Agnese and Dr. Bernard Fisher of St. Louis University have demonstrated that patients with pancreatic insufficiency due to cystic fibrosis are uniformly and profoundly deficient in vitamin E. These patients represent the best available models of human E deficiency which can be studied under controlled conditions.

The studies conducted thus far indicate that vitamin E deficiency in man is associated with many of the findings in animals, such as hemolysis (breakup of red blood cells and separation of hemoglobin from the corpuscles) and evidence of degenerative muscle involvement, but generally at a lower level.

The investigators concluded that patients with CF and secondary tocopherol deficiency should receive vitamin E supplements to correct the condition. The scientists noted, however, that there is little reason to add vitamin E supplements generally in countries such as the United States where people ingest adequate amounts of the vitamin in their diets and have normal blood tocopherol levels, despite the current public fad over vitamin E and "megavitamin therapy."

Blood Polyamines in Cystic Fibrosis

Prevention of CF is unlikely at the present time because of its mode of hereditary transmission. Although effective screening tests have been developed for some other genetic disorders, such as Tay-Sachs disease and sickle cell anemia, a simple and reliable method of detecting carriers of the CF trait so far has eluded investigators.

Recent research by NIAMDD scientists suggests that blood polyamine levels (physiologically active nitrogen metabolites) may be altered in cystic fibrosis patients and in asymptomatic carriers of the disease trait. If such an alteration were consistently demonstrable in the latter group, measurement of polyamines might serve as a CF carrier detection test.

To substantiate this theory, Drs. David W. Lundgren and Philip M. Farrell evaluated polyamine metabolism in cystic fibrosis by measuring the specific blood polyamine, spermine (Sp), and its precursor, spermidine(Spd), in CF patients and carriers. Both groups evidenced increased blood spermidine levels and decreased spermine, leading to significantly altered Spd/Sp ratios as compared to that of normal persons.

The findings thus far suggest that blood levels of polyamines are disturbed in cystic fibrosis patients and carriers. Further study, however, will be required to determine if this apparent abnormality will be useful in population screening for carriers of the CF trait. Moreover, in view of the widespread distribution of polyamines in cells and tissues, further investigations may provide an insight into the nature of the elusive basic defect in cystic fibrosis.

Early Detection

In related research, a clinician at Children's Hospital in Washington, D.C. is testing what may prove to be a reliable diagnostic tool for cystic fibrosis in newborns.

The test, developed in Germany, is based on the principle that in most CF patients the pancreas fails to secrete an enzyme necessary for protein digestion. The experimental detection test indicates the presence or absence of an excessive amount of the protein albumin in the stool, a positive result indicating the need for more extensive examination. The procedure may serve as a valuable adjunct to the standard cystic fibrosis diagnostic test, the sweat test, for excessive salt in perspiration. Although highly accurate in patients three or four weeks of age or older, the sweat test is not suitable for the newborn.

If expanded clinical trials reinforce the initial findings, the new diagnostic tool may enable doctors to initiate immediate therapy and thereby ameliorate or prevent the symptoms of CF. At present, most patients are diagnosed in early childhood, some even as late as the teens, allowing the complications of the disease to take hold. By providing physicians a possible advance warning of the disorder, the "meconium test", if promptly followed with specific treatment, may lead to significantly prolonged survival.

Cystic Fibrosis Bibliography

Through contract funds from the National Institute of Arthritis, Metabolism and Digestive Diseases, the National Cystic Fibrosis Foundation is preparing a comprehensive bibliography on the wide-ranging aspects of cystic fibrosis. The bibliography is designed to make available a consolidated listing of all scientific literature references on the subject, and to serve as an educational stimulus to physicians and investigators in the area of CF and allied health fields. The index should be available for distribution in the fall of 1975.

Outlook

Although much has been accomplished toward alleviating the symptoms of cystic fibrosis, its basic defect and means of permanent control still elude investigators. Malnutrition due to pancreatic insufficiency, formerly a serious complication of the disease, can now be readily managed in most cases by administration of supplementary pancreatic enzymes of animal origin. Through improved antibiotic therapy the consequences of chronic pulmonary disease can now be forestalled in many patients. These measures, and others, have prolonged the life of the cystic fibrosis patient, and have also enhanced the quality of that still unduly short life.

Research is now focused on a wide range of problems. These include refinement of precise screening techniques to identify carriers of the cystic fibrosis trait; identification of the underlying metabolic defect in the disorder; and improvement of antibiotic therapy to retard the progression of chronic pulmonary disease, the most frequent fatal complication of cystic fibrosis. The findings of recent years are contributing to an increasing knowledge base from which the ultimate answer to the cystic fibrosis problem hopefully will come.

DIABETES

Diabetes mellitus is a serious chronic disease which affects over 4-1/2 million Americans. Among diseases, it is the sixth leading cause of death and contributes to heart attacks, stroke, kidney failure, peripheral vascular disease, and blindness. Treatment of diabetes represents only efforts to control the symptoms of the disease. At present there is no known cure. It is essential, therefore, to continue scientific research to find a cure or identify a means of preventing its devastating long-term complications.

Diabetes research at the National Institutes of Health (NIH) is centered in the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). Six other NIH components, notably the National Heart and Lung Institute and the National Eye Institute, also conduct and support research in this field, particularly in the long-range complications of the disease. Recent significant research results include uncovering of additional evidence of a role for glucagon, as well as for the hypothalamic hormone - somatostatin - in diabetes; linking of the onset of diabetes to a prior viral infection; successful transplanting of insulin-producing beta cells in diabetic animals, and further developing an "artificial pancreas."

This ongoing research received encouragement in July, 1974 with enactment of the National Diabetes Mellitus Research and Education Act (Public Law 93-354). The Act calls for development of a long-range plan to expand and coordinate the national research effort against diabetes mellitus; to advance activities of patient, professional, and public education to alert citizens to the early indications of diabetes mellitus; and to emphasize the significance of early detection, proper control, and complications which may evolve from the disease.

Obligations for Programs in Diabetes

	1972	1973	1974	1975 Estimate	1976 Estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases	$8,182,000	$8,235,000	$12,126,000*	$12,222,000*	$13,024,000

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National Institute of Arthritis, Metabolism, and Digestive Diseases

A complicated disease, for which there is no known cure, diabetes has been known for some time to be a hereditary disorder. As a result of the body's inability to metabolize carbohydrates normally (which, in turn, is related to impaired production or activity of the hormone insulin), the diabetic patient is unable to convert dietary carbohydrates properly into the stored form, glycogen, or to utilize them normally to produce the energy required for body functions. Thus, the carbohydrates, in the form of glucose, accumulate in the blood and, because of their high concentration,

* Includes $994,000 in 1974 and $14,000 in 1975 from restorations of 1973 impounded funds.

overflow into the urine. As the disease progresses, abnormal carbohydrate metabolism becomes associated with additional derangement in the metabolism of fats and proteins.

"Juvenile Diabetes" is the severe form of the disease which is characterized by onset early in life. This classic type of severe, "brittle" or "unstable" diabetes is usually found in children or young adults with a parent or parents with diabetes or a history of diabetes in their families. If untreated, juvenile diabetes rapidly progresses to a state of grave metabolic imbalance, caused by a relatively severe deficiency in insulin output or severe impairment in insulin activity. One result may be the excessive breakdown of fat with the production of ketone acids which may lead to coma and death unless controlled by insulin administration and other supportive therapy. Patients require lifelong maintenance therapy based on daily insulin injections. This controls the more obvious clinical symptoms and permits the patient to engage in near-normal activities. Nevertheless, patients with juvenile diabetes have a decreased life expectancy and are subject to a gradual onset of progressive changes in various organ systems, the so-called long-term complications. These complications involve a specific abnormality in the small blood vessels of the body characteristic for diabetes, an accelerated degenerative process in the large blood vessels akin to atherosclerosis, and a characteristic, spotty degeneration in the nervous system. With the passage of time, these underlying pathologic processes may progressively result in one or more of the following:

(1) Premature heart attacks, strokes or impairment of the blood supply to the extremities.

(2) Kidney failure.

(3) Progressive deterioration of vision and eventual blindness.

(4) Disabling neuropathies including impotence.

Fortunately the majority of patients with diabetes are afflicted with the more common, less severe type of "Maturity-Onset Diabetes." This form of the disease, as its name implies, usually has a gradual onset in the 50's and 60's and in most cases does not require daily administration of insulin. Many of these patients benefit from reduction in body weight to normal levels. Patients with maturity onset diabetes may also gradually develop some serious long-term complications.

Diabetes is a prime example of a disease in which the research conducted by a number of the Institutes of the National Institutes of Health may be pertinent. Therefore the NIH is establishing mechanisms to ensure coordination of research by the several Institutes concerned.

Diabetes-Endocrinology Centers

In November, 1974 the NIAMDD announced the award of grants to establish four Diabetes-Endocrinology Centers to expand ongoing fundamental and clinical research efforts in diabetes and to expedite the

flow of scientific information about diabetes from the laboratory to the bedside. The institutions, geographically dispersed, are: the University of Virginia, Charlottesville; Vanderbilt University, Nashville, Tennessee; the University of Chicago, and the University of Washington, Seattle.

These Centers are being established only where a substantial, productive program in diabetes research already exists. An interdisciplinary research effort, the center concept involves many investigators from various departments within the medical schools as well as relevant departments elsewhere in the universities. Such a cooperative effort will bring valuable data from many disciplines into single focus on the problem, will bring about greater efficiency in utilization of facilities and funds, and should stimulate investigators in related areas to contribute to the diabetes effort.

Causation - The Infection Theory

Evidence has been mounting in recent years to suggest that diabetes in genetically prone individuals may be triggered by an infectious process, such as mumps, German measles, or perhaps an influenza-like virus. In some animals, under given circumstances, such viruses seem to disrupt the release of insulin or kill the insulin-producing cells. If such a virus, or viruses, ever is identified in humans, a whole new therapeutic approach to diabetes may evolve.

NIAMDD grantee Dr. Bryce Munger of Pennsylvania State University reported two years ago that healthy guinea pigs become frankly diabetic two to six weeks after being caged with diabetic guinea pigs, or after being injected with urine concentrate from their diabetic counterparts. Efforts to identify an infectious agent or its route of transmission, however, have been unsuccessful.

The infection theory has gained support from the fact that "epidemic" outcroppings of juvenile diabetes are reported periodically in certain areas. In addition, one study conducted in England has found that 85 percent of newly discovered juvenile diabetes cases were preceded by an infection.

Less than six months ago another investigator now a grant-supported scientist of the Public Health Service, Dr. Harry Sultz of the State University of New York, Buffalo, reported evidence of a link between juvenile diabetes and mumps. If substantiated, this finding might explain why new cases of juvenile diabetes appear in cycles, much like the infectious diseases of childhood.

Dr. Sultz's team of scientists reviewed case histories of 118 children with diabetes in Erie County, New York, and found that half of them had contracted mumps about four years before they showed evidence of diabetes. This finding led to a comparison of the incidence of diabetes with the incidence of mumps over a 20-year-period in Erie County. Here, the investigators also found a correlation. There were corresponding peaks and valleys on the graph of mumps cases which corresponded with the peaks and valleys on the graph of diabetes cases four years later.

From these data the investigators propose that a high incidence of diabetes in boys that occurred in Erie County between 1950 and 1960 was related to the widespread practice at the time of exposing preadolescent

boys to mumps. This practice was followed to reduce the risk of eventual sterility following virus infection of the testes, a possible complication if mumps is contracted after puberty.

Meanwhile, at the University of Vermont, a grantee of the NIAMDD and of the National Institute of Allergy and Infectious Diseases, Dr. John E. Craighead, has shown that genetic factors influence the occurrence of virus-induced diabetes in mice. He has been studying the effects of a diabetes-inducing virus - encephalomyocarditis or EMC virus - in mice of varying genetic constitutions. EMC virus produces a disease in mice which exhibits many features of human juvenile diabetes.

Mice of two different strains, when inoculated with the virus, developed systemic infections, and, in the course of the infections, virus multiplied to a similar extent in animals of both types. Mortality, however, was greater and blood glucose levels were abnormally high in one strain, while blood sugar levels remained normal in the other strain. Data obtained in further study suggest that production of diabetes by EMC virus is influenced not by a single genetic factor, but rather by several genes acting in concert.

Not all attempts to demonstrate such correlations have been successful, however. The NIAMDD Epidemiology and Field Studies Branch in Phoenix, Arizona, conducted a study on the prevalence of diabetes in the residents of the Pribilof Islands, a relatively isolated population, 5 years subsequent to an epidemic of coxsackie B4 infection, but could find no relationship between new cases of diabetes and the earlier coxsackie B4 infection. This population suffered an epidemic of mumps at approximately the same time and evaluations will also be made to examine the possible effect of mumps on the development of diabetes.

In addition, Dr. Craighead at the University of Vermont is beginning a retrospective 10-year survey and analysis of clinical records on juvenile diabetes in regard to virus infection preceding onset of diabetes in children.

Another grantee, Dr. Sidney Kibrick, Boston University, has also begun a comprehensive study to explore the relation between diabetes mellitus and coxsackie B viral infection in mice genetically predisposed to diabetes.

The results to be forthcoming in the next 2 to 3 years from these Institute-supported studies should be extremely informative in clarifying whether or not the premise of a viral origin for a proportion of the incidence of diabetes mellitus is viable.

Diabetes - A Bihormonal Disorder?

In 1971 Dr. Roger Unger, a NIAMDD grantee at the University of Texas, Dallas, reported that diabetes is characterized by excessive glucagon secretion, in addition to insulin deficiency, and thus may be a bihormonal disorder. (Glucagon, a hormone secreted by pancreatic alpha cells, stimulates release of glucose from the liver and tends to elevate blood glucose levels).

In subsequent studies Dr. Unger linked glucagon excess to infection, which often results in deterioration of blood sugar control in diabetic patients, and to diabetic ketoacidosis (increased ketoacid production) which requires emergency therapy.

Another recent study by an Institute grantee, Dr. Peter Forsham of the University of California, San Francisco, demonstrated that infusion of the hypothalamic hormone, somatostatin, into normal human subjects results in a lowering of both plasma glucagon and glucose levels. He subsequently showed that infusion of somatostatin into diabetic patients decreased plasma glucagon levels by 50 percent and plasma glucose levels by 25 percent. Moreover, somatostatin combined with insulin was more effective than insulin alone in diminishing the elevated blood glucose levels associated with meal ingestion. These research studies suggest that somatostatin, possibly in some longer-acting form, may prove to be a useful adjunct to insulin.

Meanwhile, at the University of Washington, NIAMDD grantees Dr. John Ensinck and Dr. Charles Goodner have observed that among known inhibitors of insulin or glucagon secretion, somatostatin appears to be unique in that it inhibits both hormones, whereas others inhibit selectively. The scientists, who are studying the effects of somatostatin in baboons, have issued a precautionary warning to investigators using somatostatin in human patients, however. Their preliminary studies have revealed that only a three-hour infusion of the hormone in baboons may significantly reduce blood platelets and increase the likelihood of bleeding.

With the recent discovery of somatostatin new aspects of the mechanism of the natural history of diabetes are being revealed. Recent work from Dr. Unger's laboratory has demonstrated that maintenance of normal blood glucose levels depends on the coordinated actions of both glucagon and insulin, and puts a different emphasis on the mechanism of the increased blood glucose in fasting diabetics. The reason for this fasting high blood sugar could therefore be inappropriately high glucagon levels.

Thus, glucagon and insulin provide, via their antagonistic actions upon glucose balance in the liver, a means by which glucose turnover can be changed without a major perturbation of glucose concentration.

For example, when both insulin and glucagon increase symmetrically, as happens during the ingestion of protein, both glucose production and glucose utilization increase symmetrically, but blood glucose concentration remains unchanged. Conversely, when both insulin and glucagon are decreased symmetrically (as in the case of somatostatin infusion to inhibit secretion of both hormones) the effect is a fall in both glucose production and glucose utilization, with but minor change in blood sugar levels.

Work from Dr. Unger's group has shown in experimental animals that when both insulin and glucagon are inhibited by infusion of somatostatin, normal glucose levels are maintained. Only if suppressed levels of glucagon are raised to normal by infusing glucagon does hyperglycemia (elevated blood sugar) appear. These new developments suggest that glucagon may have a far more important role in the genesis of diabetic hyperglycemia than had previously been suspected.

Transplantation of Insulin-Producing Cells

Logically, the implantation of a normal healthy pancreas in a juvenile diabetic patient should modify and ameliorate his diabetes. Although this procedure has been attempted in a number of patients with severe diabetes, the grafted organs, in every instance, eventually were inactivated by the transplant rejection reaction of the patient's immune mechanisms.

Therefore, several groups of research scientists are attempting to find a satisfactory method of transplanting only the insulin-producing, beta cells of the pancreas. It is hoped that such a procedure will result in improvement of diabetic control, as well as in prevention of the secondary complications of diabetes, such as kidney failure or vascular damage.

Two years ago, Drs. Walter Ballinger and Paul Lacy, NIAMDD grantees at Washington University, St. Louis, reported preliminary success in transplanting such cells from normal rats to diabetic rats of the same genetic strain. Transplantation into pockets in the thigh muscles or into the peritoneal cavity resulted in a temporary, significant reduction of blood and urine glucose levels, and restoration of weight gain, but the host animals still exhibited abnormal glucose tolerance.

The Missouri scientists more recently have described direct "implantation" of beta cells into the liver of diabetic rats by their injection into the portal vein. This approach has led to a marked fall in blood glucose levels and abnormal urine output, restoration of weight gain, and nearly normal results in glucose tolerance tests. Such improvement lasted for at least three months and several animals survived as long as nine months.

One recurring obstacle in such research has been the beta cell harvesting techniques, which have produced very low yields and necessitated the use of multiple donor animals for each transplantation procedure. Now the same investigators have developed a new digestion-filtration technique for isolating beta cell islets which yields sufficient islets for single-donor transplantation. Transplantation of these islets from normal Rhesus monkeys to diabetic Rhesus monkeys has resulted in significant reversal of the diabetic state in all animals. Recipient monkeys immediately became more active in their cages, and excessive thirst and urination, and elevated blood sugar levels (all symptoms of diabetes), were reduced. Intravenous glucose tolerance tests performed one week after transplantation showed significant improvement. This animal model now can be used for additional long-term studies before islet transplantation in human diabetic subjects is considered.

Another Institute grantee at the University of Minnesota, Dr. Arnold Lazarow, reported last year that diabetes had been ameliorated in adult rats following transplantation of islets of beta cells derived from immature pancreases of newly-born rats into the peritoneal cavity.

This past year, a grantee of the National Institute of Child Health and Human Development, Dr. William Clark of the University of California, Los Angeles, successfully treated diabetes in adult rats by transplanting whole pancreases taken from genetically compatible rat fetuses of gestational ages 17 to 18 days. Either complete or partial control of the

disease lasted up to 165 days in 64 percent of transplant recipients, and the tissue transplants continued to function successfully nine months after transplantation.

These successful results with fetal tissue may be due in part to a special property of the fetal tissue; however, in both instances highly inbred rats were used and one would thus expect fewer problems with immune rejection mechanisms.

A Note of Warning

As exciting as beta cell transplantation and whole organ transplantation appear to be on the surface, the NIAMDD in conjunction with the American Diabetes Association has been compelled to sound a warning about optimistic speculation in conjunction with such findings. They have cautioned that success in total or sub-total transplantation of the pancreas in humans has been "exceedingly limited" and not to be considered a form of treatment for human diabetes.

Such transplantation, including islet cell transplantation, is a highly experimental procedure and further extensive animal experimentation must be conducted to assure safety. Such research in human beings is regarded as premature because of serious problems of tissue incompatibility. Any experimentation concerning humans, it is noted, should be carried out only by research teams after review by a board on human research.

"Artificial Pancreas"

Two years ago a long-time NIH grantee at the University of Southern California, Dr. Samuel Bessman, devised a blood sugar sensor capable of continuously monitoring glucose levels in the blood and other body fluids. This accomplishment was viewed as the first practical step toward eventual development of an "artificial pancreas," an implantable device which would be controlled by an automatic blood glucose level sensing mechanism and would be capable of delivering insulin automatically to the insulin-dependent diabetic patient at the moment he needs it and in the exact dosage required.

Recent research by a number of other investigators has brought additional developments in efforts to devise a computerized, insulin-stocked "artificial pancreas." Dr. Stuart Soeldner of the Joslin Diabetes Foundation, Boston, for example, has implanted a glucose sensor in monkeys and has kept one there for as long as four months before rejection occurred. In rats and rabbits, futhermore, he has wired the sensor to an implanted, tiny radio transmitter with which to transmit outside the body continuing information on blood sugar levels.

Meanwhile, Miles Laboratories, in collaboration with the University of Toronto, has produced a laboratory "artificial pancreas" for use in hospitalized diabetic patients. This device monitors blood sugar levels and dispenses insulin or glucose as required. Thus far, it has been used successfully on nine hospitalized diabetic patients in West Germany.

In Toronto, a second prototype of the same device has undergone successful clinical trials in a dozen juvenile diabetics. University of Toronto scientists, led by Dr. A. Michael Albisser, designed and developed the artificial organ's complex hardware, while Miles Laboratories

incorporated the entire device into a single unit. It must be emphasized, however, that these experimental devices are interesting and useful laboratory machines of large size to which the patient must be connected, and he must remain in a restrictive hospital setting as long as he receives his experimental and temporary treatment.

Most of the investigators involved in such research now estimate that it will require many years before a fully miniaturized, implantable artificial pancreas, which will work effectively and for more than just brief periods of time, will be ready for human clinical trials.

Juvenile Diabetes in Remission

Juvenile diabetic patients who are dependent upon insulin and who are prone to develop ketoacidosis are generally characterized by rapid onset of their illness and by nearly complete failure of the insulin-producing pancreatic beta cells. Temporary remission of diabetes occurs in one of five such patients, however, shortly after disease onset.

In recent studies of this poorly defined remission state NIAMDD grantee Dr. Stuart Soeldner of the Joslin Diabetes Foundation has found that most patients in remission show substantial insulin release responses to glucose and to meal ingestion, and near-normal responses to administration of insulin. His findings support the concept that clinical remission in such cases of recently emerged juvenile diabetes is dependent on a functional recovery of the insulin-producing beta cells, and indicate that the significant "insulin resistance" of severe diabetes is not present in this early remission state.

Knowledge that a functional recovery of the beta cell and unimpaired insulin sensitivity play important roles in the maintenance of the clinical remission state may lead to several new research approaches to the problems presented by diabetes.

Complications of Diabetes

As noted earlier in this report, despite apparent control of the obvious clinical symptoms of diabetes, progressive changes apparently occur inexorably, especially in juvenile diabetes, that may lead to gradual deterioration of blood vessels, kidneys, the nervous system and the eyes. Thus, a great many investigations are devoted to learning more about these serious complications and, hopefully, to preventing them.

For example, NIAMDD grantee Dr. Donald McMillan of the Sansum Medical Research Foundation, Santa Barbara, California, has recently reported that serum viscosity is significantly increased in diabetic patients compared to both healthy subjects and patients with diseases other than diabetes. Moreover, this increased serum viscosity is even greater in diabetic patients with clinically detectable small blood vessel disease. Dr. McMillan suggests that the observed increase in serum viscosity might be a part of the metabolic disturbance of diabetes, and that it could play a role in the development of diabetic microangiopathy, or small blood vessel disease.

Studies being conducted at New York Medical College, meanwhile, point towards new ways of decreasing the incidence of damaged blood vessels in diabetics. In a strain of mice with genetic diabetes, Dr. Rafael Camerini-Davalos, an Institute grantee, has reduced the occurrence of kidney complications by half, from 80 percent to 40 percent, by treating the mice with pyridinolcarbamate. By contrast, the occurrence of kidney complications among untreated diabetic mice ranged from 67 to 85 percent.

Treatment with the new drug apparently normalized the activity of a specific enzyme - glucosyltransferase - in the liver, the activity of which had been significantly increased prior to such therapy. This increased enzymatic activity appears to be one of the first abnormal steps in the blood vessel damage caused by diabetes. If such increased activity of this enzyme is inherited in human subjects as it is in the mice studied by Dr. Camerini-Davalos, then he and his associates have observed for the first time a mechanism for the possible prevention of blood vessel damage resulting from diabetes.

Outlook

Diabetes gained renewed national attention in 1974 with passage of the National Diabetes Mellitus Research and Education Act. This legislation calls for a broadening of diabetes-related activities, including the preparation of a National Diabetes Plan, in the near future. A yearly report to the Congress will continue to give an accounting of NIH's research activities. At the rate at which diabetes research is and has been proceeding in recent years, it can be hoped that deferment of its onset in predisposed persons and suppression of its severe complications are within the realm of possibility.

EMPHYSEMA AND CHRONIC BRONCHITIS (CHRONIC OBSTRUCTIVE PULMONARY DISEASE)

Because the progressively crippling lung diseases, emphysema and chronic bronchitis, usually occur together, they are known collectively as "chronic obstructive pulmonary disease" (COPD). Together, they afflict 7.8 million Americans and, each year, kill approximately 28,000.

In emphysema, alteration of normal lung architecture leads to increased resistance to airflow and progressively more difficult breathing. Chronic bronchitis is characterized by persistent inflammation and swelling of the bronchial airways, excessive production of mucus and other fluids that tend to block the airways and that lead to coughing, spitting, and shortness of breath.

Federally supported research, training, and control activities directed against emphysema and chronic bronchitis are carried out by a number of agencies of the Department of Health, Education, and Welfare.

The National Heart and Lung Institute bears primary responsibility for conducting, supporting, and coordinating basic and clinical research to increase the store of medical knowledge of the structure and function of the pulmonary system and to develop improved methods for the prevention, diagnosis, and relief of chronic lung diseases. The NHLI programs are coordinated with those of the National Institute of Allergy and Infectious Diseases--which has strong research programs in acute pulmonary infectious diseases and allergies that may operate in the development of chronic lung diseases or complicate their clinical course--and the National Cancer Institute, whose programs focus on pulmonary malignancies. The National Institute of Environmental Health Sciences, National Institute of Child Health and Human Development, National Institute of Arthritis, Metabolism, and Digestive Diseases, and the Division of Research Resources also support some research projects bearing on emphysema and chronic bronchitis.

The Bureau of Community Health Services of the Health Services Administration also supports research on these diseases, but their primary emphasis is on working at the regional, state, and local levels to encourage the application of existing knowledge to case finding and to the treatment and rehabilitation of those afflicted. Diagnosis, treatment, and rehabilitation are also prime concerns of the Bureau of Medical Services of the Health Services Administration.

The chronic respiratory diseases constitute an exceedingly complex problem demanding a broadly based, diversified approach. In the aggregate, the efforts of these agencies constitute such an approach and insure that each of the many aspects of the problem will be adequately explored.

Obligations for Emphysema and Chronic Bronchitis (COPD)

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health:					
National Heart and Lung Institute.....	$5,000,000	$5,592,000	$7,723,000	$6,700,000	$6,850,000
Health Services Administration:					
Bureau of Community Health Services.....	2,875,000	1,230,000	---	---	---
Bureau of Medical Services.....	1/	1/	1/	1/	1/
Total.....	7,875,000	6,822,000	7,723,000	6,700,000	6,850,000

1/ Not identifiable.

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National Heart and Lung Institute

Strictly speaking, emphysema and chronic bronchitis are separate disease entities and, as such, occur separately in relatively distinct form in some patients. However, they are considered together in this report because they usually occur together, and, indeed, it is often impossible to determine which of the two is the most important contributor to disability in a particular patient. Both emphysema and chronic bronchitis appear to involve many of the same physical and biochemical components within the lung, and to invoke many of the same physiological mechanisms found there. This is reflected in common usage of the collective term "chronic obstructive pulmonary disease" (COPD), which is largely synonymous with emphysema and chronic bronchitis.

During Fiscal Year 1974, National Heart and Lung Institute support of research and training activities directed against emphysema and chronic bronchitis amounted to $7,723,000. This amount is an increase of approximately $2.1 million over the preceding year. The money was used for intramural research investigations in Institute laboratories, the funding of grants and contracts for research and development projects in medical institutions and industrial laboratories throughout the country, and related administrative costs.

Most of this research is administered by the Institute's Division of Lung Diseases (DLD), and involves approximately 20 percent of the DLD budget. Additional NHLI research bears only indirectly on the chronic obstructive pulmonary diseases per se, but nevertheless promises to contribute substantially toward the prevention, diagnosis and treatment of these disorders and their complications, and to enhance our understanding of the underlying disease processes. An example is the development of blood oxygenators and ventilatory devices for providing short-term support during respiratory crises.

Research areas bearing on emphysema and chronic bronchitis include:

- studies aimed at defining the causes of COPD, still poorly understood.
- development of diagnostic techniques for evaluating pulmonary blood-flow and gas exchange in the lung.
- development of reliable techniques for evaluating lung function and for early detection of chronic lung diseases.
- development and evaluation of drugs for relief of the distressing symptoms of emphysema and chronic bronchitis, including respiratory stimulants, mucolytic or mucus-dissolving agents, and bronchodilators to widen or dilate air passages.
- development of respiratory-assist devices, blood oxygenators and related techniques for the treatment of acute respiratory failure.
- research seeking more effective means of coping with circulatory complications of chronic lung diseases, such as pulmonary hypertension, right-heart failure, and secondary polycythemia (increase in number of circulating red blood cells).
- development and use of organ, cellular, and subcellular living systems for the study of synthesis and breakdown of collagen and other connective-tissue components of the lung.

Magnitude of the Problem

Chronic obstructive pulmonary disease is a serious health problem in this country. In 1973, it killed 28,000 Americans; each year, direct and indirect costs of COPD amount to approximately $1.8 billion and 90,000 man-years of lost productivity. Latest available statistics indicate that, of 1.3 million Americans who have emphysema, 700,000 are under age 65. In terms of disability payments by the Social Security Administration, this disease category ranks third, exceeded only by coronary heart disease and schizophrenic disorders. Chronic bronchitis afflicts 6.5 million Americans; 180,000 citizens are limited in activity as a consequence of the disease.

Chronic Bronchitis

Chronic bronchitis is characterized by a persistent inflammation and swelling of the linings of the bronchial airways, excessive production of mucus (phlegm) and other fluids that tend to block the airways and that lead to coughing, spitting, and shortness of breath. The onset of chronic bronchitis may be slow, and usually follows episodes of acute bronchitis. Early symptoms are often shrugged off as "smokers cough" and "winter colds." By the time the condition is diagnosed, the delicate lung tissue may be irreversibly damaged and the patient well on the way to respiratory disability. The principal known factors contributing to the prolonged bronchial irritation of chronic bronchitis are smoking, air pollution, and recurrent respiratory infections. And these same irritants can promote the development of the companion disorder, emphysema.

Emphysema

The exact cause of emphysema is not known, but the initial event appears to be a breakdown in the thin coating of mucus and the many hair-like cilia that line all air passageways throughout the respiratory system. This lining normally protects lung tissues against inhaled dust, bacteria and other harmful materials. The constant waving motion of the cilia acts to propel these particles on a mucus-lubricated path toward the throat where they can be eliminated from the body.

With the breakdown of this protective lining, the noxious materials begin to destroy the normal physical properties and architecture of the lung, producing large, inefficient air spaces. As a result, resistance to air flow increases and breathing becomes progressively more difficult.

Late in the disease, blood oxygen levels decrease, and the toxic gaseous waste product, carbon dioxide, accumulates. Death usually results from heart failure (the heart is overworked in a vain attempt to meet body oxygen needs by more vigorous pumping of oxygen-poor blood), or from suffocation during a respiratory crisis precipitated by a cold or other respiratory infection.

Diagnostic Techniques

Emphysema and chronic bronchitis develop so insidiously that many victims are unaware that anything is seriously wrong until 50 percent or more of their lung function has been destroyed. Since, at this late stage, the damage cannot be undone, development of reliable pulmonary function tests for early detection of COPD is an urgent need. Ideally, these tests should be simple, should not require elaborate equipment, nor be beyond the capabilities and the means of every physician.

In recent years, NHLI-supported research has contributed to development of many useful tests to detect and assess deterioration in lung function. Also developed have been catheterization techniques for measuring blood pressures in the pulmonary arteries and radioisotopic techniques for evaluating lung perfusion and for localizing and evaluating the extent of lung damage. These sophisticated procedures are usually available only in large, well-equipped clinical centers.

An important test for early detection of pulmonary diseases or for screening of large numbers of people has been developed which uses a simple, rapid, single-breath test of lung volume and gas exchange. The NHLI has recently awarded a new series of research contracts to further develop and apply these tests.

Another recently developed single-breath test--the determination of "closing volumes" as an index of premature obstruction of small airways--appears, on the basis of preliminary data, to be a sensitive, easily-applied technique for detecting early lung function changes in cigarette smokers who are otherwise free of respiratory disease symptoms. Current studies employing the test are aimed at standardizing the procedure and at understanding what the abnormal test results mean in terms of existing disease and the likelihood of subsequent irreversible lung damage.

Despite much progress in recent years toward the development of smaller, more portable medical devices, including pulmonary diagnostic equipment, results of a recent NHLI-supported study indicate the need for more rigorous performance-testing of certain of these instruments. The study revealed serious inadequacies in the performance of four types of electronic spirometers as compared with their more cumbersome prototypes, conventional water or bellows spirometers used to measure various parameters of lung volume. All of the electronic spirometers were found to be inaccurate and three lacked facilities for calibration. The investigators obtained evidence suggesting that the devices were advertised and sold without adequate specifications or clinical trial. Reasoning that the reliability of diagnostic equipment is as important to patient welfare as the reliability of drugs, the scientists recommend the establishment of a National Medical Devices Standards Council, and the formation of a Center for Respiratory Device Evaluation.

Treatment

Present therapeutic measures are aimed at arresting or slowing the progress of COPD, relieving distressing symptoms, improving the patient's general physical condition, and helping him to make the best use of whatever lung function he has.

Bronchodilators are widely used to make breathing easier for victims of emphysema and chronic bronchitis. Usually administered by inhalers, these drugs help to open up constricted air passages.

The surgical removal of large bullae--localized, balloon-like sacs in the lung that can trap large volumes of air and greatly interfere with normal lung expansion--has benefitted selected patients suffering from the bullous form of emphysema.

Steroids, which help to suppress inflammation, are sometimes helpful in clearing inflamed, congested airway passages and in reducing the intensity of allergic reactions. Unfortunately, steroid therapy is ineffective in many COPD patients and is frequently attended by undesirable side effects. The most serious adverse effect is a lessening of the patient's resistance to pulmonary infections.

A number of effective expectorant drugs have become available during recent years. These help to liquefy viscid mucus clogging the air passages so that coughing can clear the passages. Chronic coughing contributes to the discomfort of COPD, but physicians are understandably reluctant to administer sedative agents to suppress the cough reflex, for these may also depress breathing, with potentially dangerous results.

Portable oxygen devices have been developed to meet special oxygen needs resulting from exertion or mild-to-severe episodes of breathlessness in ambulatory patients. In selected patients, continuous oxygen therapy may be desirable to improve exercise tolerance and the potential for physical rehabilitation.

Severe distress in victims of far-advanced COPD may be helped by an intermittent positive-pressure breathing apparatus. Careful monitoring of blood gases provides a reliable check on the effectiveness of therapy.

Training utilizing breathing exercises helps victims of emphysema make better use of their limited vital capacity, and enables them to resume activities formerly beyond their endurance. For example, evidence gained from one NHLI-supported study indicates that operant conditioning--praise and token rewards given to emphysema patients for extending their breath-holding ability--can increase their tolerance to carbon dioxide and thus also increase their capacity for physical activity, since carbon dioxide build-up diminishes work capacity. Similarly, general physical conditioning, with exercises tailored to the limitations of the patient, may help.

Respiratory stimulants which act on nerve centers in the brain or chemoreceptor mechanisms in the lung or elsewhere to increase respiratory drive are under study. Several promising agents have been developed, but clinical experience with them is limited.

Intermittent antibiotic therapy has proven valuable for protecting patients against respiratory infections. The patient with chronic lung disease may also benefit from protection by influenza vaccination, especially during the winter.

Presently, relatively little can be done for victims of far-advanced COPD, but much research is directed toward development of efficient, low-cost blood oxygenators for acute respiratory failure.

An important goal of the NHLI Division of Lung Diseases is the development of improved artificial "lungs," or blood oxygenators for heart-lung machines, and for use with heart-assist devices in patients requiring circulatory support and temporary respiratory assistance. This is often needed by victims of massive heart attacks or with heart conditions resulting from or complicated by chronic respiratory disorders such as COPD. The aim is to develop blood oxygenators with high gas exchange efficiencies that cause little damage to blood, are light, compact, easily sterilized, and disposable.

Several promising models are under development, each attempting to avoid direct contact between blood and gaseous oxygen or air and all seeking to minimize damaging, turbulent bloodflow. The most promising type is the membrane oxygenator, which interposes between the blood and air an artificial membrane permeable to blood gases, eliminating a direct blood/gas interface. Its gentle blood-handling characteristics make it suitable for providing respiratory assistance over prolonged periods--up to a week or more in several reported instances--by which time many acute respiratory crises have run their course. Membrane oxygenators of at least four designs are now available for clinical use.

NHLI scientists recently developed a method of casting very thin membranes without the pinhole defects that have occasionally caused membrane failure in oxygenators. Flawless silicone rubber membranes less than one thousandth of an inch thick can be produced by this technique. The defect-free membranes, incorporated into a spiral-coil membrane oxygenator previously developed at NHLI, have shown excellent gas-exchange and blood-compatibility characteristics during prolonged periods of blood-oxygenation in animal experiments.

The NHLI is currently conducting nationwide clinical trials, with the collaboration of nine medical research institutions, of the safety and efficacy of extracorporeal membrane oxygenation in acute, potentially reversible respiratory crises.

Also under investigation is the feasibility of intermittent or continuous respiratory support with an external blood shunt and a portable membrane lung. The arterio-venous blood shunt used in these animal studies is similar to the procedure used successfully for years by patients who require periodic cleansing of their blood with an externally-located artificial kidney machine.

Limited progress is being made toward effective means of storing and transplanting lungs. From 1963 through December 1974, the American College of Surgeons/NIH Transplantation Registry recorded 35 human lung transplants, most of them performed under emergency circumstances in moribund patients. Indications for these lung transplants included carcinoma, emphysema, silicosis, pneumonitis, and proliferative bronchiolitis and alveolitis.

Death occurred in most patients within 10 days and sometimes within hours of the operation, usually because the transplanted organ or lobe failed to assume its normal function. The longest survivor exhibited acceptable lung function for 10 months, but finally died of chronic tissue rejection.

In addition to rejection and storage problems which plague all types of transplanted organs, the proper functioning of the transplanted lung depends, to a large degree, upon neural, biochemical and other regulatory mechanisms that normally control organ function. Problems inherent in the physiology and anatomy of the lung present formidable obstacles to lung transplants. The lung, because it is directly exposed to the air, is always an open door to infection even in the presence of its natural defense systems. The transplanted lung, its natural immunological defenses compromised by drugs to prevent rejection, is

especially susceptible to infection. Moreover, graft rejection episodes are difficult to detect in the transplanted lung. It is hoped that these and other technical problems may eventually be overcome through animal experimentation.

Prevention

Although the causes of COPD are still poorly defined, two factors--cigarette smoking and air pollution--are strongly suspected of contributing importantly to the development of emphysema and chronic bronchitis in both their "pure" and combined forms, and aggravating their clinical course. Emphysema, for example, is 13 times more prevalent among cigarette smokers than among non-smokers and the death rate from emphysema among smokers is 7 times that of non-smokers. Numerous epidemiological studies have established a relationship between levels of air pollution and illness and death from chronic respiratory disorders.

A study involving more than 1500 male telephone workers in four areas of the eastern United States and one area of Japan suggests that cigarette smoking plays a more important role than air pollution in the development of chronic respiratory disease. Physical examinations, which were repeated five to six years later for the American workers, revealed that respiratory abnormalities were more frequent with increasing age and with increasing numbers of cigarettes smoked per day, but were not associated with the birthplace, previous or current home address, or place of employment of the men studied.

An NHLI grant-supported epidemiologic survey among 246 coke oven workers at the Kaiser Steel Corporation, Fontana, California, recently assessed the contribution of cigarette smoking, occupational and genetic factors to the development of industrial bronchitis. Eighty-one men (33 percent of all workers) had respiratory symptoms, and in half of these men, the symptoms were consistent with a diagnosis of chronic bronchitis. In the overall group the severity of symptoms was related to cigarette consumption, but smoking did not account for all cases of chronic bronchitis. In subgroups of the subjects, severity of symptoms was also related to a specific inborn enzyme deficiency or family history of chronic bronchitis, and to type and duration of work on the ovens. Considered together, work, smoking and family history accounted for 40 percent of the variability in the severity of symptoms of chronic bronchitis, indicating that the workers represented a range of susceptibilities to the development of bronchitis. The NHLI grantees suggest that "If susceptible subjects can be identified during pre-employment screening and are effectively excluded from hazardous occupations, some cases of chronic bronchitis may be prevented."

The Institute is supporting an epidemiological survey of environmental and other factors which may account for differences between mortality in England and the United States from chronic pulmonary disease and coronary heart disease. The British death rate from coronary heart disease is substantially lower than that of the United States, but the mortality rate from chronic lung disease is much higher.

Population studies indicate that certain persons may be genetically predisposed to chronic lung disease. A hereditary deficiency of an enzyme called alpha-1-antitrypsin appears to predispose some individuals to the development of a kind of emphysema and may make them more susceptible to the harmful effects of cigarette smoking than normal subjects. The deficiency is most pronounced and the risk highest in those in whom genetic information leading to a lack of the enzyme has been inherited from both parents. But the risk may still be substantial in those who inherit the deficiency from only one parent, a group which may comprise some 5 percent of the population.

If the progression of lung disease can be prevented in these antitrypsin-deficient subjects by avoidance of smoking and exposure to lung irritants, then a means of detecting these subjects may have value. However, the recent discovery of variant forms of hereditary antitrypsin deficiency indicates the necessity for detailed studies of the distribution and disease-producing potential of each variant form before any large-scale screening and disease control programs can be undertaken.

Other Research Efforts

The Institute conducts or supports a large volume of research concerned with lung structure and function; neural, hormonal, chemical, and mechanical factors affecting respiration; gas transport and gas exchange; the destruction, repair, and regeneration of lung tissue; and the causes, clinical physiology, diagnosis, and treatment of chronic pulmonary disease.

Basic studies in respiratory physiology, by helping to clarify the role of the central nervous system and other factors in respiratory drive, may provide clues to the development of improved treatment of COPD. Other studies, centering on the various secretions of the lung, may lead to more effective mucolytic agents and expectorants for relieving clogged airway passages.

The fact that at least some forms of antitrypsin deficiency can apparently interact with environmental factors to cause emphysema has led to the theory that one or more of the proteases--protein-dissolving enzymes normally inhibited by antitrypsin in the lung--are responsible for the lung damage in this particular type of emphysema. These potentially destructive substances include trypsin and other proteolytic enzymes produced by the body as well as proteases of plant and bacterial origin. Most of the available evidence implicates the proteases released by white blood cells (leukocytes) as they do battle with bacterial and particulate lung pollutants. NHLI grantees have shown that leukocytic proteases are capable of digesting animal and human lung tissues. Furthermore, this proteolytic damage proceeds at a much more rapid rate in lung tissue obtained from antitrypsin-deficient persons, but can be retarded by incubating the lung tissues in normal serum.

Substantiation and further refinement of this theory hold the promise of correcting certain well-characterized forms of antitrypsin deficiency by: 1) stimulating increased production or release from storage sites of antitrypsin in the body; 2) correcting the deficiency by injections of antitrypsin, or 3) administering a synthetic antiprotease to counteract the damaging effects of a particular protease.

According to another theory, advanced on the basis of preliminary clinical evidence of variations in leukocyte protease activity, the clinical expression of COPD associated with alpha-1-antitrypsin deficiency may be determined in part by the degree of leukocyte protease activity; that is, some individuals with antitrypsin deficiencies may be protected from COPD by the simultaneous inheritance of low levels of the proteolytic enzyme(s) normally counteracted by antitrypsin.

By 1973, methods became available for dispersing lung tissue into mixed populations of individual cells, but in such cultures the value of biochemical studies is limited because of the complexity of the cell types in the lung.

NHLI grant-aided scientists at Albert Einstein College of Medicine, New York, have developed a method of lung cell isolation which, for the first time, enabled tissue culture studies of a single type of lung cell. The isolated cell-type (granular pneumocyte) is one of more than forty different known types of lung cells (more than is found in any other organ of the body), and is a source of a surface-active lipid substance, called pulmonary surfactant, necessary for normal lung expansion.

This significant research advance is being extended by other investigative teams in efforts to determine the precise functions and roles of other lung cell-types in health and disease.

Similar cell culture model systems, along with whole organ explants and even cell-free systems have been developed in the NHLI Division of Intramural Research in a broad research effort focused uniquely on the production and destruction of collagen in the lung.

Collagen is a principal constituent of the connective tissue "cement" that binds together the cellular components of organs and tissues. It is the most abundant protein in lung, comprising 10 to 15 percent, by weight, of normal lung tissue in adults and is fundamental to lung structure and function. Lung connective tissue figures prominently in a number of pulmonary disorders. In emphysema and related disorders, an important factor appears to be the breakdown of collagen or other connective tissue components, with subsequent disruption of the functional units of the lung (alveoli) where gas exchange occurs. In the so-called interstitial lung diseases, which account for about 20 percent of chronic lung conditions, the problem appears to be excessive collagen and connective tissue production and subsequent development throughout the lung of fibrous (scar) tissue that interferes with normal breathing.

NHLI research is directed at learning more about collagen production in the lung and about the mechanisms that control the process. The studies indicate that the lung produces as many as four different forms of collagen, three of which have been characterized. One of these resembles the collagen of cartilage, a second the collagen of skin, and a third the collagen found in the aorta and, possibly, other large arteries.

During fetal development, collagen production accounts for about 4 to 5 percent of total protein synthesis in the lung. During the newborn period, this figure rises to 14 percent and the collagen concentration in lung tissue increases, indicating a shift of emphasis in lung protein synthesis toward collagen production. By adulthood, collagen synthesis has returned to the 4 to 5 percent level and there is no further accumulation of collagen in the lung. The studies are attempting to define the mechanisms by which collagen synthesis is "turned on" during the period of maximal lung development, then gradually "turned off" as the lungs attain maturity.

The NHLI investigators have developed a cell-free system in which the cellular components required for the synthesis of collagen and other lung proteins are extracted from homogenized lung tissues of various origins, then combined in varying proportions to synthesize collagen in the test tube. Finally, enzymatic techniques have been developed for breaking down the connective tissue framework of lung tissue, so that individual cells are dispersed into appropriate media, whence the various cell types may be segregated, harvested, and then grown in culture to determine their role (if any) in collagen synthesis and to assess the effects (if any) of various chemical stimuli on the rate of synthesis.

Further development and continued use of these model systems should greatly enhance our understanding of the processes involved in connective tissue synthesis and destruction, and may lead to therapeutic measures for stimulating the repair or regeneration of lung tissue damaged or destroyed by emphysema and related lung disorders or to measures for preventing or slowing down the lung fibrosis resulting from other lung diseases.

A disease resembling emphysema sometimes develops spontaneously in horses and has been under study by NHLI grantees, but COPD does not occur naturally in any other common laboratory animal. There is urgent need to develop additional animal models for studying COPD and for evaluating preventive

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HEALTH SERVICES ADMINISTRATION

Bureau of Medical Services

In FY 1974, this program treated 1,602 inpatients and 2,551 outpatients for pulmonary disorders, and related chest diseases in its eight general hospitals and 26 outpatient clinics. 1/

Three hospitals located at New Orleans, San Francisco, and Staten Island have inhalation therapy clinics and maintain complete clinical services which engage in treatment, research, and training activities related to emphysema and other pulmonary diseases. The five hospitals without specialty service in pulmonary diseases, however, do engage in limited research activities and offer clinical treatment.

Some of the research activities currently in progress are:

1. The Effect of Hemodynamic Stress on Pulmonary Intra- and Extra-vascular Fluid Volume.

2. Rifampin-Isoniazid Treatment of Concurrently Active Tuberculosis and Lepromatous Leprosy.

1/ Workload is based on primary diagnosis data. It does not include patients where secondary diagnosis is respiratory diseases.

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or therapeutic measures. As mentioned above, treatment of lungs with proteolytic enzymes provides an emphysema-like lung injury model. The enzymes used in some of these studies are obtained from the wandering leukocytes and macrophages found in the lung.

Conclusion

Although COPD emerged only in recent years as an important health problem, and one that remains largely unresolved, increased awareness, concern and active research hold forth promise of effective prevention, diagnosis and treatment. Annual mortality statistics reflect a slight reduction in deaths due to emphysema and chronic bronchitis. But, because some of the causative or aggravating factors are found in the very air we breathe, the concerted efforts of many segments of society will be required if we are to significantly reduce the toll of death and disability exacted by these insidious diseases.

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THE EPILEPSIES

The epilepsies are chronic brain disorders which are characterized by brief episodes of loss of consciousness, uncontrolled movements, and erratic behavior in various combinations. These manifestations are called epileptic seizures and are known to result from intermittent paroxysmal firings of nerve cells in the affected area of the brain. The manifestations reflect the functional characteristics of the affected area.

Estimates place the number of persons in the United States who have epilepsy at between two and four million and the cost of their disabilities to the Nation at approximately $4.25 billion a year. Of that total, about $325 million is spent by the Federal Government for aid, rehabilitation, benefits, medical assistance, and veterans care and about $85 million is spent by state and local governments for special education and other programs. Approximately one percent of the total funds--some $4 million--goes to research.

Drugs or surgery provide effective therapy for prevention of seizures in about 60 percent of epileptic patients and hence enable them to live relatively "normal" lives. Control of attacks is partial or absent in the other 40 percent of patients. As few as one or two brief attacks a year can make it difficult, often impossible, for patients to obtain work or a driver's license. Persons who have frequent seizures have difficulty existing without help. Complete control of all seizures and effective rehabilitation are important goals.

The Department conducts and supports basic and clinical research into the causes, prevention and better treatment of the epilepsies. A large area of such research is the development of more effective and less toxic anticonvulsant drugs in order to increase the number of completely controlled cases. This research is supported by the National Institute of Neurological Diseases and Stroke (NINDS) of the National Institutes of Health (NIH).

Obligations for Programs in the Epilepsies

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health					
National Institute of Neurological Diseases and Stroke	$5,007,000	$4,035,000	$5,610,000	$4,317,000	$,5,115,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

Background

The human brain is constantly in a dynamic state of activity, receiving information or input from the entire body and from the outside world relayed by way of the sense organs and the sensory nerves. The information is evaluated, processed, stored for future reference, and acted upon by the output through the body's network of motor nerves and muscles.

Underlying these processes are the basic mechanisms which are responsible for the generation by brain cells (neurons) of impulses of electrochemical energy which sweep rhythmically along the neuronal networks. When a task is to be performed, the neurons which control the relevant part of the brain or body transmit impulses until the job is done and then "turn off." In some cases such as epilepsy, certain neurons begin sending impulses to perform some action but when the work is finished do not shut off the transmission. During such periods of unwanted neuronal discharges, parts of the body receiving the impulses may function erratically and the brain may even cease conscious operation, although motor activities can continue without apparent purpose. Often other groups of adjacent neurons join in and send additional unintended impulses for the duration of the overflow. Brain areas are termed "epileptic" when these episodes of uncontrolled discharges happen repeatedly, and the erratic alteration of consciousness and the body's fitful physical movements constitute the "seizures."

Seizures may be simple partial, usually without loss of consciousness, and consisting of an eyelid flicker, shaking of a finger or hand, jerking of the corner of the mouth, an unpleasant feeling in the stomach, dizziness, unusual or distasteful sights, sounds, smells or tastes. They may be complex partial, usually with loss of consciousness, during which the afflicted person appears to be in a dreamy state, at rest or moving automatically and purposelessly. To the observer, the patient may seem to be experiencing fear, anger, elation or irritability, although there is usually no recollection of any emotions upon recovery from the seizure.

Seizures are termed generalized when most of the brain becomes involved; then unconsciousness occurs and both sides of the body react. In milder, generalized seizures called absence (old term, petit mal), eyes blink or turn upward and contact is lost momentarily. In more severe types called tonic-clonic (old term, grand mal), there can be complete body involvement with intense, alternate muscle rigidity and relaxation. Other kinds of generalized seizures are tonic (rigid muscles), clonic (spastic muscles), myoclonic (jerking muscles) or akinetic (collapsed muscles).

Some seizures start as partial and progress to generalized, as the malfunctioning cells in a restricted brain area recruit other cells and the paroxysmal discharges spread throughout the brain and out to the body.

Seizures may occur frequently or only rarely. They last from a split second to several minutes and may be preceded by "auras" (or warnings) and are usually followed by periods of confused exhaustion. In "status epilepticus," seizures occur so close together that they appear to be continuous and in rare instances may end in death if not arrested by appropriate therapy. Although a number of mentally retarded persons have epilepsy, most people who have epilepsy but no other brain involvement are as intelligent proportionately as the general population and have similar intellectual and earning potentials.

Causes

Brain damage appears to be a basic precursor to development of the epilepsies. Seizures often develop following difficult births, chronic severe drug or alcohol addiction, head injuries, high fever and some infectious diseases. In man, seizures can be caused by accidental or surgically-associated brain injuries. In animals various chemical or electrical stimulation used experimentally can produce seizures. Seizures are often concomitant of brain tumors, abscesses or congenital malformations. Where no history or evidence of possible brain damage exists, the epilepsy is termed idiopathic (cause unknown).

Epilepsy is not contagious. The epileptic patient is not insane. In a small percentage of patients with certain epilepsies the susceptibility may be hereditary. More than half of the seizure patients are under 20 years of age. Yet, anyone, at any age, may become a victim as a result of brain injury.

Available Therapy--Drugs and Surgery

Potassium bromide was used to treat epilepsy from the 1850's until 1912 when phenobarbital was found effective. Dilantin, developed in 1938, and phenobarbital are still the most effective and generally safest drugs for controlling seizures. From 1960 until 1974, there were 13 standard drugs on the market for oral use in the long-term treatment of epilepsy. Several of these when injected intravenously, are useful for stopping "status epilepticus." In 1974 as a result of the cooperative efforts by Institute scientists, the FDA, and the drug company which developed it, the drug carbamazepine (Tegretol) was approved by the Food and Drug Administration for long-term treatment of epilepsy. This was the first new antiepileptic drug to be introduced in 14 years. Another, clonazepam (Clonopin), is now under consideration for approval, and several others are currently under active clinical investigation. Surgery is occasionally useful to treat focal seizures. It is indicated, however, only in cases with frequent poorly controlled seizures that are sufficiently localized that removal of the affected brain area will not cause additional epileptic damage or impair other functions. Studies on patients during such surgery have proved invaluable in improving our understanding of normal and abnormal brain functions.

Need for Research

Discovery and continuous refinement of anticonvulsant drugs have greatly improved the chances for victims of epilepsy to lead normal lives. But more research and greater application of research findings are needed in order to answer several problems.

Those whose seizures are controlled must be considered normal, just as diabetics controlled by insulin are considered normal. These persons, and others whose seizures are not incapacitating, are entitled to educational, occupational, insurance and social opportunities equal to those enjoyed by others. Treatments for the more handicapped must be improved so that they, too, may achieve social and financial independence. And finally, the epilepsies must be eliminated as a health problem.

Research Tools

The electroencephalogram (EEG), recorded by electrodes pasted on the scalp (or in some experimental cases implanted in brain cells), is used to locate the beginnings of the epileptic discharge, and as it progresses, to measure the intensities and durations of the brain waves. Telemetering or mobile equipment, which can be worn by the patient during routine activities holds the EEG electrodes in place and transmits the EEG readings to a receiver-tape recorder. Seizures are accurately recorded and can be reviewed repeatedly or fed into computers for analysis of brain-wave patterns. Computers are helpful in efforts to develop seizure-warning devices and in the interpretation of electroencephalograms or brain wave recordings. Seizures similar to those experienced by man can be induced in animal models, by electrical, chemical or sensory stimulation, so that new drug and surgical treatments can be evaluated. Gas Liquid Chromatography (GLC) technique measures levels of antiepileptic drugs in patient's blood, permitting physicians to maintain effective therapeutic, non-toxic levels, verifies whether or not medications are being taken as prescribed; and compares drug effectiveness and patient responses. Because there are large variations among the GLC measurements by clinical laboratories, NINDS has contracted for means to establish testing standards.

Epilepsy Research Centers

Epilepsy research centers are supported by the Institute at the University of California at Los Angeles, the University of Washington, the University of Wisconsin and Yale University Medical School. Each center focuses on specific research aspects--basic, drug mechanisms, animal models, and drug and surgical treatment of patients--generating knowledge about brain mechanisms and

functions, and developing new techniques[4] for treatment. Additionally, the NINDS is supporting over 100 epilepsy research projects in 14 states and five foreign countries.

Perinatal Research

Since 1959, NINDS-supported medical centers have collected data on mothers and babies in over 50,000 pregnancies. This has been a comprehensive effort to learn more about the causes of many neurological disorders, including the epilepsies, that begin before birth, at birth, or within the first eight years of life. The Collaborative Perinatal Research Project has ended its data collection this year, with the completion of examinations at the eighth year for about half of the project's total of 40,000 children. As the data analyses are completed (1976), new clues about the epilepsies and their causes are expected to be revealed.

Drug Research

In a recent review of 250 clinical studies that purported to show efficacy of various anti-epileptic drugs, only 110 gave evidence for any experimental design and only three had been subjected to statistical evaluation. To overcome this lack of objectivity in establishing the respective values of standard and experimental anticonvulsants, the Institute's Collaborative and Field Research Program is now conducting or supporting the majority of the Nation's research in this area. This clinical research is guided by an NINDS Advisory Committee on the Epilepsies comprising specialists from medical schools, the drug industry, and government.

Cooperative exchange of drug research information between drug companies and the Institute's programs keeps the Advisory Committee's Subcommittee on Anticonvulsant Drugs abreast of progress and helps industry decide whether or not to start lengthy and costly human or animal trials.

As a result of Institute-industry exchange, data from NINDS studies of the drug carbamazepine (Tegretol) at the New Castle State Hospital, New Castle, Indiana, were included in the CIBA-GEIGY Company's application to the Food and Drug Administration (FDA) for that drug's approval for epilepsy treatment (see Research Progress).

Similarly the Roche Company has had available the Institute-supported studies in their application for approval of clonazepam (Clonopin) as an anti-epileptic agent (see Research Progress).

NINDS-supported studies have also contributed to the introduction of a new syrup formulation for Zarontin (ethosuximide) by the Parke-Davis Company.

The Abbott Company, the FDA and NINDS together have reviewed information on dipropylacetic acid sodium (Depakine) over the last three years, with the resulting decision by Abbott to obtain the rights to the drug which has been used extensively in Europe and Japan for 10 years. The Institute is initiating clinical evaluation of its efficacy in treating generalized absence seizures.

Chlorazepate dipotassium (Tranxene), another Abbott Company anticonvulsant, is being investigated for use against complex partial seizures.

Mexiletine (Ko 1173), used in Europe as a drug for cardiac arrythmias, is being investigated by the Institute for possible use as an adjunct with other drugs to aid in control of various seizure types.

An American pharmaceutical company, which does not presently market any anti-convulsants but is concerned about the need for better epilepsy-treatment drugs, is developing an antiepileptic agent which is in early animal-testing stages.

As a result of guidance from the NIH[5] Advisory Committee on the Epilepsies, the University of Virginia and the Medical College of Georgia are comparing Zarontin with Clonopin in control of generalized absence seizures. Early results show about the same effectiveness. The study continues and a pilot study of Depakine will begin soon.

The New Castle State Hospital has finished evaluations of the effects of combined doses of phenobarbital, Dilantin and Tegretol on intractable generalized tonic-clonic seizures. Data obtained are being analyzed. Studies have started on Ko 1173 to establish its efficacy and safety when used in combination with other drugs.

At the University of Washington, an 18-month study continues comparing efficacy and safety, respective drug levels and effects on behavior of Tegretol and Dilantin when used for complex partial seizures. Preliminary studies of Tranxene are under way and other researchers are comparing effects of several standard and experimental drugs on complex partial seizures in animal models.

Last year a study of the psychological and EEG effects of Tegretol in treating complex partial seizures conducted at the Lafayette Clinic, Detroit, Michigan, showed that the drug had no apparent psychological benefits and although it did control seizures it did not normalize the EEG. The second phase of the study now underway, evaluates the combined effects of Tegretol and Mysoline (primidone) on seizures, behavior and EEG's.

A University of Kansas pilot study is continuing to ascertain whether the number of post-traumatic epilepsy cases can be reduced by immediate and extended treatment of head-injury victims with Dilantin and phenobarbital.

In the Institute's Collaborative and Field Research pharmacology laboratory, scientists continue to study how the brain is affected by antiepileptic drugs, how drug combinations work and how to measure blood levels of the new experimental drugs being tested in patient-study populations. The NINDS unit offers blood-level measuring services to other researchers and guidance to laboratories that provide blood-level measurements commercially. An agreement has been concluded with the National Bureau of Standards for developing standards for laboratory blood-level measurement standards over the next two years.

The NINDS Anticonvulsant Drug Development Program, begun in 1968, continues its efforts to find more effective, less toxic antiepileptic drugs. A new screening program has been added. The intent is to identify existing compounds which have previously unrecognized anticonvulsant properties, to commit industry and government resources to develop them into effective treatment drugs, to stimulate synthesis of new anticonvulsants, and to establish an accessible computer-based data resource for all compounds tested.

Under a two-year contract, Abbott Laboratories is synthesizing a new series of organic compounds and evaluating them for potential anticonvulsant effects so that the best candidates may be selected for further study. Since June 1973, some 35 compounds have been synthesized and tested, with several showing impressive anticonvulsant activity. When the project ends in July 1975, the best selections will undergo further evaluation.

Comprehensive Epilepsy Program

The Institute's Comprehensive Epilepsy program is currently in the feasibility studies stage. Eleven studies are scheduled for completion in June 1975. It is planned to establish up to two Comprehensive Epilepsy Centers in Fiscal Year 1975 to provide support for epilepsy-related clinical research and for coordination of teaching and health-care delivery services in a given geographical area by means of complementing and extending existing services.

Experimental Animal and Clinical Studies

It is generally agreed that studies of the epilepsies have revealed more about the functioning of the human brain than have any other disorder. The epilepsies afford neurologists unique opportunities to examine brain mechanisms and study of factors which elucidate seizure mechanisms.

In searching for types of early brain damage which may cause seizures in later life, scientists have turned to the effects that drugs and infantile febrile (fever-caused) convulsions have on the brain in its early stages of development.

In experiments with rats that were brain damaged shortly after birth by electrical stimulation, it was found the brains were smaller and had lesser amounts of vital chemicals at given ages, and the animals were slower learners than control rats whose brains were not harmed. Their resistance to drug-induced seizures was lower than that of the controls. Another epilepsy researcher examined brains of numerous children who had experienced febrile convulsions before death, and concluded that although the portions of brain cells called dendrites are damaged by any convulsions, they are particularly vulnerable to febrile convulsions. This investigator believes that deterioration of dendrites is a factor in producing or predisposing seizure activity. Although conclusions differ as to precisely which structures are decreased or damaged, it appears that febrile convulsions probably decrease the number of neurons or deform them so that they are subsequently susceptible to seizure discharges.

For a number of years, investigators have been seeking information about possible roles of neurotransmitters in seizure activity. A neurotransmitter is the chemical messenger discharged on impulse from one nerve fiber ending to transmit the impulse for either stimulation or inhibition in a second cell. Among the neurotransmitters are the compounds called monoamines. In recent animal experiments on the mechanism of action of anticonvulsant drugs, it was found that drugs which deplete the monoamines in the brain often lower its resistance to experimentally-induced seizures, whereas effective anticonvulsants like Dilantin and phenobarbital raise the levels of the compounds and increase resistance to seizures. Such fundamental correlative studies are continuing.

Treatment--Drugs

In the past five years, full development of technology--especially gas-liquid-chromatography (GLC)--for measuring blood levels of antiepileptic drugs has greatly improved seizure control for many epilepsy patients. Numerous articles about the importance of blood-level measurements in managing patients have been published. Two of the country's leading epilepsy researchers, one at Cornell University Medical School in New York City and the other at NINDS, have compiled all the important aspects of the usefulness of measuring blood levels of antiepileptic drugs in an Editorial Review in the Archives of Neurology. They emphasize that measurements of blood levels facilitate the establishment of individual dosage regimens, reveal irregular drug intake by patients, quickly identify which drug is causing side effects in cases of multiple drug therapy, and provide clues as to which patients may metabolize the drugs abnormally. The authors also provide a tabular summary of the pharmacologic properties of five common anticonvulsants for easy use by physicians. The authors advise that doctors should not adjust blood levels arbitrarily on the basis of quantity alone. This review is expected to facilitate the delivery of better health care for those who have epilepsy.

A California company has developed a new method for measuring blood concentrations of Dilantin and phenobarbital. The developers use antibody and enzyme reactions to obtain measurements which are said to be as accurate as other previously-used methods. Other advantages, verified by researchers from Columbia University College of Physicians and Surgeons and the Cornell University Medical

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Center, are accuracy, reproducibility, speed and the small size of samples needed (five tests can be made with a thimbleful of blood). It has been termed a "valuable adjunct in the detection of anticonvulsant drugs."

Another new method for measuring drug levels, using saliva rather than blood, is in experimental stages at the University of Washington under an NINDS contract. Levels of four drugs--phenobarbital, Dilantin, Tegretol, and Mysoline--were measured in the same individuals at the same time using different specimens--saliva, spinal fluid and blood. For Dilantin and Tegretol, the levels determined by the saliva corresponded accurately with those in blood and spinal fluid samples. Mysoline and phenobarbital did not correspond. The saliva method will be valuable as a clinical check against blood measurements where adverse side effects or lack of control are out of proportion to blood levels. Another advantage is the ease with which samples can be obtained.

In 1968, initial reports indicated that children of epileptic mothers taking anticonvulsants are at greater risk for birth defects. Numerous studies since have borne out the contention. This year, scientists at the Mayo Clinic in Rochester, Minnesota, evaluated 12 studies that have been reported on epileptic mothers and their children and published results of their own study. Their findings were consistent with the others, namely that there is an increased incidence of malformation--particularly cleft palate and heart disease--at birth in the children of mothers who take anticonvulsants during pregnancy. They conclude that there is still not enough evidence to incriminate a specific type of epilepsy or any single drug. The authors estimate that at least 2,000 births will have to be studied to detect malformation-incidence rates. At present there is agreement that the risk to mother and fetus is likely to be greater if anticonvulsant treatment is stopped than if seizures are controlled by continued treatment.

Treatment--Surgery

The surgically-implanted cerebellar-stimulating device which was hailed by the press last year as a "brain pacemaker" received much scientific attention this year. Although the new procedure seemed to have helped several patients, its use has raised more questions than it answered. Will changes occur in the brain from implanted electrodes and the constant stimulation and, if so, will they be harmful or permanent? Early indications are that the answers to these questions are in the affirmative. Can control be maintained over a long period? What if stimulation is turned off? What if it is not turned on? After a year of related studies on five patients at the NIH Clinical Center, personnel of the NINDS Surgical Neurology Branch doubt that the method represents any sort of long-term "cure" for any type of the epilepsies.

Prognosis-Diagnosis

One question about epilepsy which still awaits clarification concerns the effects that febrile convulsions exert on the infant brain to cause epilepsy later and what treatment is best to stop those convulsions and lessen chances of epilepsy occurring. Now, a researcher from Copenhagen has reported on nearly a lifetime of work with febrile convulsions in a volume, Supplement 32 to the Electroencephalography and Clinical Neurophysiology. She presents a number of conclusions.

Among the conclusions, the outcome after febrile convulsions depends mainly on how promptly the seizure is controlled. The risk of occurrence depends on the age, sex and family history of febrile convulsions. Subsequent epilepsy usually starts within a few years but may not start until as long as 25 years after the original insult. From one to 20 percent of children who were observed beginning with the first attack subsequently developed epilepsy. The initial seizures are "psychomotor" or "temporal lobe" alone or with grand mal in the great majority of cases. In 10 to 25 percent of the cases, the subsequent

seizures are petit mal, suggesting that febrile convulsions and petit mal epilepsy may be related forms of convulsive disorders. Treatment consists of stopping the febrile convulsion at once, the most effective agent now being diazepam (Valium). The underlying illness and its complications need to be corrected, as in any illness without convulsions. Prophylactic treatment involves removing the sources of infection, preventing new febrile illnesses and preventing high temperatures with new febrile episodes. Well controlled tests show that phenobarbital is effective prophylactically when blood levels of the drug are maintained at therapeutically-effective levels, and medication must be faithfully taken until the age of four. This study is considered an outstanding contribution to epilepsy research and should find wide use.

A report on petit mal (absence) epilepsy made by a French scientist to the French Branch of the International League Against Epilepsy in Paris in December, 1973, offered some new evidence on prognostic features. The report on 213 children showed that with an onset of seizures between five and nine years of age and with no other form of seizure present and with normal intelligence, the outlook is favorable for eventual disappearance of seizures. An onset before age five is often associated with mental retardation; an onset after age ten is associated with persistence of absence attacks and appearance of generalized tonic-clonic seizures. Causative factors and EEG characteristics had no prognostic value.

Public Opinion

The American Institute of Public Opinion has taken its sixth survey in the past 25 years to determine attitudes about epilepsy expressed by the adult population of the United States. Released in May, the survey showed great improvement in those attitudes. Some knowledge about epilepsy was reported by 90 to 95 percent of the people interviewed. When those who know about epilepsy were asked if they would object to their children playing with epileptics, the upward change in percentages of those without objection, from 1949 to 1974 was from 57 to 84. When asked if they thought epilepsy is a form of insanity, those who did not increased from 59 to 86 percent. On whether epileptics should be employed, affirmative answers went up from 45 to 81 percent. Adverse responses were proportionately reduced. Most favorable opinions were from the better educated and employed, younger and urban members of the population. Factors believed to contribute to the improved attitudes include: overall change in attitudes to all dread diseases, improved control of seizures, educational efforts, employment of epileptics by some major industries, and more reasonable laws for epileptics concerning immigration, marriage and operation of motor vehicles.

Communications

Scientific Information Exchange

Knowledge acquired from research is valuable only when disseminated to other scientists and physicians who can apply it to treating patients. To insure communication of epilepsy-research results the Institute has taken a number of actions.

1. NINDS has been instrumental in publishing the proceedings of a Workshop on the Neurosurgical Treatment of Epilepsy through Raven Press. The workshop held in December 1973, comprised papers by international leaders in neurosurgery. Those papers should prove widely useful to neurologists, neurosurgeons, and others dealing with epilepsy.

2. NINDS has published an Epilepsy Bibliography 1900-1950 with key word and author indexes in a computer system developed by the Institute during the last five years. A total 11,825 citations are classified and numbered.

3. NINDS continues partial funding of the monthly Epilepsy Abstracts, now in its seventh volume. It is used by over 1,000 subscribers who pay Excerpta Medica $40 a year to help defray costs of publication and mailing.

4. NINDS sponsored meetings in March and August 1974 of the Subcommittee on Anticonvulsant Drugs which reviewed progress of NINDS-sponsored research contracts and proposals for continued and additional studies.

5. NINDS produced and put into distribution through the National Medical Audiovisual Center (for loan) and the National Audiovisual Center (for sale) a motion picture "The Absence Seizure." The film shows every type of absence seizure with its EEG patterns and emphasizes the importance of recognizing and understanding absence seizure characteristics so that specific therapy can be applied. More than 510 loans and 58 sales of the film have been made during 1974.

6. NINDS has contributed significantly to publication of a paper which establishes principles for clinically testing antiepileptic drugs. Appearing in Epilepsia, it is intended to improve the quality of clinical data collected internationally on antiepileptic drugs so that new epilepsy drugs can be more rapidly developed and precisely used than heretofore. Institute representatives attended an international symposium on the subject in Copenhagen, in September, 1974, an indication of increased interest in Europe.

7. NINDS surveyed research support for epilepsy in the U.S. for FY 1973. Of more than $5.3 million expended on epilepsy research, NINDS funded 51 percent of all projects and provided 67 percent of all funds. Other agencies within the Department of Health, Education, and Welfare supported an additional 38 percent of projects with 21 percent of funds. The other 11 percent was funded by the Veterans Administration, the Department of Defense, the National Science Foundation, and the Epilepsy Foundation of America. Research into causes and treatment received most support. There has been a dramatic increase in neuropharmacologists and pharmacologists active in epilepsy research.

8. NINDS has contributed some 15 lecturers, who are authorities in epilepsy, to medical groups nationally and internationally. Dr. J. Kiffin Penry, of the NINDS staff, has been chosen the Secretary General of the International League Against Epilepsy to serve until its next Congress in the Netherlands in 1977 and has been elected President of the American Epilepsy Society for 1975.

Public Information

The Institute responded to requests for 16,167 pamphlets, monographs, and magazine reprints on the epilepsies from the scientific, medical, paramedical, and lay public. For the public inquiries, the materials included Epilepsy, Hope through Research in both English and Spanish and NINDS Research Program Reports 1974. For scientists, monographs entitled Epidemiology of the Epilepsies; The Clinical Neurophysiology of Epilepsy--A Survey of Current Research; Epilepsy--A Review of Clinical and Basic Research; Blood Level Determination of Antiepileptic Drugs--Clinical Value and Methods; and a pamphlet of literature citations on Blood Level Determinations of Antiepileptic Drugs. Newspaper and magazine articles, health columns, radio and TV anouncements and TV appearances by Institute scientists also generated interest in the publications and work of the NINDS.

HIGH BLOOD PRESSURE (HYPERTENSION)

High blood pressure (hypertension) affects an estimated 23 million American adults. Of these, about 14 million have hypertensive heart disease (chiefly heart enlargement) resulting from the elevated blood pressure. The prevalence of high blood pressure among U.S. blacks is about twice as high as that among whites, and the prevalence of hypertensive heart disease among black males is nearly three times that of white males. Nearly 15 million Americans with high blood pressure are under age 65 and more than 4 million are under 45.

Thanks largely to the availability and widespread use of effective drugs for blood pressure control, the U.S. death rate from high blood pressure has declined by nearly 65 percent since 1950. But the disease still claims over 20,000 deaths a year directly and contributes to hundreds of thousands of deaths from heart attacks and strokes, because it increases susceptibility to these events, the No. 1 and No.3 causes of death. In addition, high blood pressure places an added burden on the heart that may ultimately drive it into failure and may stress or damage arteries and the organs they supply throughout the body. The kidneys are highly vulnerable to such damage, and kidney failure is a common complication of severe hypertension.

High blood pressure alone roughly doubles the risk of coronary heart disease. The threat is amplified by the presence of other risk factors. For example, if the person with high blood pressure is a cigarette smoker, his risk from coronary heart disease is increased by a factor of 3.4. If, in addition, he has elevated blood fats, his risk is more than 10 times that of persons with none of these risk factors.

Obligations for programs in hypertension

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health:					
National Heart and Lung Institute	$27,446,000	$28,261,000	$42,506,000	$39,110,000	$40,865,000

NATIONAL INSTITUTES OF HEALTH
National Heart and Lung Institute

HYPERTENSION

When the physician determines blood pressure with the familiar blood pressure cuff, he records two numbers. The higher of the two (expressed in millimeters of mercury) is called the systolic blood pressure. The lower number represents the pressure persisting in the arteries while the heart relaxes and refills between beats (diastole) and is called the diastolic blood pressure. The upper level of normal systolic pressure in adults is considered to be around 140, the upper level of normal diastolic pressure around 90; this would be recorded at 140/90.

Most investigators consider a diastolic pressure of 90 to be the upper limit of normal. Diastolic pressures between 90 and 95 are called "borderline" by some investigators, and a diastolic pressure that persistently exceeds 95 is hypertension by definition of the World Health Organization. The Data Base Task Force of the National High Blood Pressure Education Program agrees that persons with blood pressure above 160 systolic and/or 95 diastolic should be referred to a physician for evaluation of their condition.

What Causes High Blood Pressure

In only about 10-20 percent of persons with hypertension can any specific organic cause be identified to account for their elevated blood pressure. The remaining 80 to 90 percent are said to suffer from "essential" or "primary" hypertension, the cause of which is not known. An important consideration in diagnosis is distinguishing between "essential" and "secondary" forms of hypertension. For unlike essential hypertension, which can be controlled but not cured, secondary hypertension can sometimes be cured if its underlying cause can be identified and eliminated. Such causes include various forms of kidney disease including the narrowing of blood vessels to the kidney, various hormonal excesses, and narrowing of the aorta (called coarctation).

Unfortunately, not all patients with secondary hypertension are cured, even when the underlying cause has seemingly been identified and eliminated. But even incurable cases of secondary hypertension can often be controlled with blood-pressure-lowering drugs.

A widely held belief concerning essential hypertension contends that any of a number of factors may operate in the development of the disease and in its various phases. This is called the "mosaic theory". The factors that initiate high blood pressure may not necessarily be those that sustain it, and factors of greatest importance at one stage of the disease may not be dominant during other stages.

Many victims of essential hypertension develop the disease during their thirties. During the early stages of the disease, it seldom produces any symptoms perceptible to the person who has it, and the absence of noticeable symptoms may persist until the disease is well advanced. If undetected and untreated during its early or middle stages, the disease may enter an accelerated phase, sometimes called "malignant hypertension," in which the victim's blood pressure, previously high but relatively stable, climbs sharply to levels that pose an immediate threat to his survival. The accelerated phase usually occurs when the disease has already produced some blood-vessel damage in the kidneys.

Treatment of High Blood Pressure

The specific drug or drug combination used by the physician varies with the severity of the disease and also with the patient's response to the medication prescribed. No single agent is uniformly effective in all patients or against every phase of hypertension, but where one drug fails, another drug or drug combination will usually succeed, so that only in rare instances does it prove impossible to control the patient's blood pressure at least to some degree.

These agents are not without side effects, especially in higher doses. With some drugs, the side effects are relatively mild and work no hardship, neither impeding the patient in his job nor his other pursuits. However, the most potent antihypertensive drugs, called ganglionic blocking agents, may cause undesirable side effects, including blurred vision, bladder dysfunction, constipation, and sexual impotence in males. Fortunately, side effects can usually be minimized by using several agents in combination, each in relatively low doses. The effect of such regimens on blood pressure are cumulative, but the side effects associated with each specific drug are attenuated.

Minimizing side effects is of special importance in the treatment of high blood pressure because even relatively mild side effects can become bothersome to patients faced with the prospect of remaining on medication indefinitely. They may be especially annoying to the patient with high blood pressure who had experienced no symptoms until his doctor started treating it.

The benefits of therapy in reducing illness and mortality from stroke, heart failure, and kidney failure have been convincingly demonstrated among patients with diastolic pressure above 105. Although evidence from epidemiological studies indicates that even mild hypertension increases the individual's risk of coronary heart disease, stroke, and other cardiovascular disorders, the probable benefits of blood pressure control are more difficult to verify because it requires larger periods of observation and larger numbers of patients followed under controlled situations to observe sufficient numbers of significant complications.

High blood pressure is easily detected in the physician's office. Yet, probably because the disease seldom produces early symptoms that send the afflicted person to his doctor, epidemiologists believe that many American adults with high blood pressure do not know that they have it and others who know about their high blood pressure may not be taking any treatment for it. This is not always the physician's fault. Some patients are reluctant to take pills for something that is seemingly causing them no problems. Others, unaware of the need for continuous therapy, stop taking their pills because they feel better; and still others stop because some side effect of the pills makes them feel worse.

Current Research Efforts

The Institute currently supports more than 200 research projects, at universities and medical centers all over the country, concerned with the etiology, pathogenesis, prevention, diagnosis and treatment of high blood pressure and with related subjects, such as kidney disorders and physiology. In addition, the Institute also conducts research in its own laboratories at Bethesda.

Principal research areas in the hypertension program include:

- The search for causes of essential hypertension, and identification of genetic and environmental factors that increase susceptibility to the disease or aggravate its clinical course. Without such knowledge, cures or effective means of prevention are unlikely.

- Evaluation of drugs and other therapeutic procedures for blood pressure control and assessment of the effects of these measures in reducing illness and death from hypertension and such complications as heart attacks, strokes, congestive heart failure, and kidney failure.

- The role of the autonomic nervous system, hormones, and other biologically-active substances in regulating blood pressure.

- Diagnosis and treatment of hypertension secondary to kidney disorders, endocrine disorders, and certain tumors.

- The treatment of severe kidney disease through kidney transplants, and artificial kidneys.

- The role of the kidney and its secretions, such as renin, kallikrein, and prostaglandins in blood pressure control.

- Kidney mechanisms operative in maintaining fluid balance, electrolyte balance, and acid-base balance, and disturbances in these mechanisms that may underlie or result from hypertension.

- Identification of innovative methods to educate professionals and the general public about all aspects of hypertension (National High Blood Pressure Education Research Program).

The Institute also supports Specialized Centers of Research on hypertension at Cornell, Harvard, Indiana and Vanderbilt Universities, and the University of Tennessee. These centers are attacking high-priority problems, including:

- Studies to determine whether abnormalities of the renin-angiotensin-aldosterone system that often occur in hypertension are predictive of the severity of the disease, the nature of the blood-vessel damage, or the response to drugs that lower blood pressure.

- The effects of hypertension on bloodflow and blood-vessel structure in the renal, coronary, and cerebral circulations.

- Development of a non-human primate model of essential hypertension.

- Development of improved techniques for assaying and tracing the metabolism of certain hormones, peptides, and other substances involved in blood pressure regulation or suspected of involvement in initiating or sustaining the hypertensive state.

- Genetic and behavioral factors in essential hypertension.

- The role of the kidney and of fluid and electrolyte disturbances in essential and secondary hypertension.

- Studies on hypertension secondary to kidney disease, toxemia of pregnancy, and certain endocrine disturbances.

- Studies on the causes, diagnosis, and clinical management of malignant hypertension.

Other definitive information will be provided by the NHLI Hypertension Detection and Follow-up Program which is established in 14 clinical centers where some 11,500 patients aged 30 to 69 with diastolic pressure exceeding 95 at initial screening are being followed. The goal is to assess the effectiveness of antihypertensive therapy in controlling high blood pressure and the extent to which disability and death from its complications can be reduced. An important

secondary goal is to overcome problems in motivating patients with high blood pressure to seek treatment and to adhere faithfully to the prescribed therapeutic regimens. Over 160,000 persons were screened to obtain 11,500 participants. For those who have been observed one year or longer and have been seen within the last four months at the clinic, according to their latest record, 73 percent have achieved their goal blood pressure. The goal blood pressure is between 80 and 90 for the diastolic blood pressure, depending upon baseline blood pressures.

Because high blood pressure often co-exists with other cardiovascular disease risk factors, such combinations can sharply escalate the threat to the life and health of affected persons. It has been estimated that 80 percent of death and disability from cardiovascular disease occurs among persons having one or more of the following: high blood pressure, elevated blood fats, and the cigarette habit. Two or more of these risk factors are often present in the same individual, and these persons run 3 to 10 times the risk of those with none. Now getting underway is the NHLI Multiple Risk Factor Intervention Trial, which will evaluate the effectiveness of countermeasures against these three risk factors among high-risk males aged 35 to 57. Recruitment of the approximately 12,000 study participants will be completed in 1975 and the clinical phase of the trial in 1980.

National High Blood Pressure Education Program

In an effort to combat some of these problems, NHLI is participating in an educational effort involving both Federal and private organizations. The National High Blood Pressure Education Program, which was initiated in 1972, is aimed at alerting both the medical profession and the public as to the dangers of high blood pressure and the beneficial effects of therapy.

Although the National Heart and Lung Institute has been designated the lead coordinating agency, the National High Blood Pressure Education Program (NHBPEP) is emphatically pluralistic and enjoys the support and cooperation of some 15 Federal agencies, as well as approximately 60 national organizations and virtually all state health departments. Participants include important professional organizations (American Medical Association, National Medical Association, American Hospital Association, American Osteopathic Association, American Heart Association), voluntary health agencies, the insurance industry, the drug industry, minority and consumer groups, labor unions, industrial organizations and corporations, educational organizations, and others. The activities of this cooperative, multidisciplinary group encompass a wide range of efforts in education, research, planning, and services on both national and local levels.

The Program currently supports a variety of experimental efforts to determine cost-effective ways of achieving high blood pressure awareness or behavior change in the public, patients and health professionals, with particular emphasis on effective patient education to promote compliance with treatment. In addition, special studies are examining employer practices with regard to hypertensive employees, automated blood pressure measuring devices, and analysis of the cost-benefit ratio in treatment of hypertension.

Consumer education efforts include creation of a mass media campaign featuring popular celebrities (Jimmy the Greek and Ann Landers), and distribution of materials to TV, radio and mass circulation magazines and newspapers, resulting in a minimum of $4.1 million in free public service television time and $640,000 in free radio time for NHBPEP messages to date.

Activities in professional education include development and dissemination of recommendations for detection, treatment and patient education, development of professional educational materials (including patient education films), and close liaison with key professional organizations and medical standard setting groups (National Board of Medical Examiners, American Board of Internal Medicine,

Professional Standards Review Organizations Program). In cooperation with the NHBPEP, the Food and Drug Administration has awarded a contract for a national survey of physicians' attitudes, knowledge and self-reported behavior regarding hypertension, to establish baseline data regarding hypertension awareness and action.

Program services include a High Blood Pressure Information Center which responds to public inquiries, develops and evaluates educational materials; distributes, free of charge, educational materials produced by the Program and other organizations, operates a Speakers' Bureau for local, state and national meetings, and manages a vigorous exhibit program which has taken the Program's recommendations to 46 professional and non-professional meetings. A Community Consultation Service has provided on-site need assessment and technical assistance in planning and implementing hypertension control programs to more than 200 communities to date, and averages 25 new contacts with local communities per month.

National High Blood Pressure Month has been established to focus national attention, through a specific target date, on the need for hypertension detection, control, and education programs and to provide a rallying point for state and local activities. Efforts generated by the first month (May 1974) resulted in screening of approximately half a million persons and referral of approximately 76,000 persons with elevated pressures to their physician through the coordinating and educational efforts of numerous local community programs. Media coverage reflected a 140 percent increase in newspaper articles during the month's activities.

Although it is too early to assess changes in the health status of the population as a result of NHBPEP efforts, some changes in health activities can already be seen. Not only did the number of physician visits for hypertension increase sharply from 58,454,000 in 1972 to 70,804,000 in 1973, but the rate of increase, particularly for first visits, also rose significantly. In 1972, total visits for hypertension increased 13 percent over the previous year, while in 1973 the increase was 21 percent. The increase for first visits was 7 percent in 1972, and 21 percent in 1973. The increase in physician visits was paralleled by an increase in antihypertension prescriptions filled during the same periods. New prescriptions rose 31 percent in 1973 over the previous year, and refills jumped 29 percent. Data from the Health Interview Survey and the Health Examination Survey of the National Center for Health Statistics will also be used to evaluate overall Program impact.

Conclusion

Although medical science can neither prevent essential hypertension nor cure it, research over many years has yielded a large body of information about blood pressure control mechanisms and some of the derangements that occur. It has led to the development of many drugs for controlling high blood pressure of all degrees of severity and agreement that such drugs can save and prolong lives among patients with moderate to severe high blood pressure. It has yielded effective means for identifying potentially curable secondary forms of high blood pressure and for searching out persons most likely to benefit from surgery or other definitive therapy. It is to be hoped that continued research will yield safer, more effective drugs for blood pressure control, eventually lead to cures where now only palliative measures exist, and ultimately to the elimination of high blood pressure as a significant cause of illness, disability, and death.

7
APPENDIX

National Institutes of Health
National Heart and Lung Institute

HYPERTENSION

The Drugs for Hypertension

Combinations of drugs are often necessary to maximize the blood pressure-lowering effect while minimizing the side effects. Therapy must be individualized, with good communication and teamwork between physician and patient, until the right therapy is found. Since about 1950 these drugs have brought revolutionary improvement in treatment of hypertension and prospects of patients for a full and rewarding life span.

Diuretics are now a mainstay, and have largely replaced the rigid salt-free diets of a few years ago, which many patients found unendurable. Working directly in the kidney to induce urinary sodium excretion, diuretics reduce the total volume of body fluid outside the cells, including that of blood plasma, and also conteract the edema which swells the tissues of those whose hearts are already failing for any reason. Irrespective of whether there is edema, with the loss of salt and fluid from the body there is generally mild loss of weight and a drop in blood pressure.

Chlorothiazide and hydrochlorothiazide, derivatives of benzothiadiazide, were the first effective oral diuretics to be introduced for hypertension, in the early 60's. They cause a sustained drop in pressure and, if treatment is continued, dilate the blood vessels and reduce resistance to peripheral blood flow and cardiac output, this facilitating the decline in pressure. Several newer benzothiadiazide derivatives, or "thiazides" -- some of greater diuretic potency -- have also been developed. Chlorthalidone is a thiazide-like diuretic which has a longer action and can be taken once a day. All of these carry some risk of depleting body potassium along with the sodium. This side effect often necessitates supplementary potassium intake. Unchecked potassium depletion may cause abnormal muscular irritability and weakness including dangerous heart rhythm disturbances. Another occasionally worrisome side effect is retention of uric acid, which may produce gout in some patients. Diabetes may also be aggravated, in some patients.

Spironolactone and triamterene are non-thiazide diuretics with the advantage that they conserve precious potassium while eliminating sodium and producing a similarly gratifying drop in blood pressure. Triamterene also acts directly on the kidney; but spironolactone is an aldosterone antagonist, and thereby represents an exceptional and interesting mechanism of diuretic action. This drug is related to one of the natural steriod hormones secreted by the adrenal gland, so that it successfully competes for the hormone's position on receptor sites in the body, thus cancelling the function of the natural hormone, aldosterone, to conserve salt and water. The synthetic analog does not have this activity; hence, sodium and water are lost from the tissues by "competitive inhibition." This type of mechanism has potential for development of other similar drugs, and a number of variations on spironolactone have already been found. The side effects of spironolactone are similar to some of the secondary actions of aldosterone, and slightly resemble the principal actions of the other two adrenal cortical hormones. Thus it may have some "sex-hormone" and "cortisone-like" effects, among others.

Rauwolfia compounds such as reserpine are long-acting drugs, usually effective against mild to moderate hypertension, especially when used in combination

with diuretics. Reserpine reduces sympathetic nervous activity by depleting norepinephrine stores at sympathetic nerve terminals. Norepinephrine is the chemical transmitter released by sympathetic nerves to convey their impulses to artery-constricting muscles and other target organs. Reserpine has a direct effect on brain centers, so the drug has a sedative or tranquilizing effect as well. Cardiovascular authorities tend to doubt this sedation has much to do with the blood pressure reduction and many regard it as an annoying side effect. Clinical depression occurs in a small minority of patients. But in combination with other drugs, rauwolfia compounds are extremely valuable against essential hypertension.

Recent reports of studies which found an association between breast cancer and use of reserpine are not conclusive. Further evaluation and investigation by the Federal Drug Administration are underway. It has been proved that reserpine in combination with a diuretic and hydralazine can reduce deaths, strokes and other related morbidity among hypertensive patients.

Hydralazine acts directly on the cardiovascular system, causing widespread dilation of small peripheral vessels, and decreasing resistance to flow, especially in arterial beds. This allows the cardiac output to increase while the blood pressure falls. This resulting "hyperdynamic" cardiac and circulatory state sometimes involves secondary problems, but these usually are not prohibitive. However, angina attacks may be worsened in patients who already have coronary symptoms, and pressure in the pulmonary artery may be increased in patients with heart valve abnormalities. Despite many different side effects (most of them negligible or controllable by varying drug combinations) hydralazine is regarded as a firstline drug for moderate to severe hypertension.

Ganglionic blocking agents such as mecamylamine and pentolinium may be used to control blood pressure in very severe hypertension that fails to respond to guanethidine and methyl dopa. These agents strike at both the sympathetic and parasympathetic divisions of the autonomic nervous system, but their use is always attended by so many undesirable, often intolerable, side effects that they are largely being displaced, as more acceptable drugs are developed. Very frequently, however, blood pressure can be controlled by using ganglionic blocking agents in combination with thiazide diuretics and other medication. One of the ganglionic blocking agents, trimethaphan, is fast acting. Given intravenously, it lowers acutely dangerous high blood pressure and is useful for hypertensive emergencies.

Diazoxide is another swift and powerful intravenous antihypertensive of great value for acute hypertensive crises. Closely related to the thiazide diuretics, it is not a diuretic; on the contrary, even while the blood pressure drops, diazoxide causes sodium and water to be retained -- an unwanted, seemingly paradoxical, side effect.

Clonidine is another potent drug recently approved for use in the U.S. Its mechanism of action calls for more study, especially since it seems to reduce cardiac output, which might become excessive if clonidine is given in combinations with other drugs that do this. Its antihypertensive effects seem to be due at least partly to unique central nervous system actions. This is promising, and there are suggestions from preliminary trials that its blood pressure effect will combine nicely with that of the diuretics.

Beta adrenergic blocking agents such as propranolol are also finding a place in hypertension therapy. Propranolol works by reducing the heart's rate and force of contraction, so that its output falls off. Although blood pressure seems to fall smoothly, and without apparent side effects, there are questions about its ultimate value in hypertension which more research is needed to answer. A randomized trial comparing propranolol with standard antihypertensive therapy is currently underway and will be completed in FY 76. The study is supported by the Veterans Administration and NHLI.

KIDNEY DISEASE AND ARTIFICIAL KIDNEYS

Chronic, or end-state, kidney failure is the common final event of many different kidney diseases. While methods are being developed to save and extend the lives of many people with end-stage kidney disease, some 60,000 Americans die annually from irreversible kidney failure. The kidneys play a central role in maintaining body functions and the body's internal chemical equilibrium. They remove end products of metabolism from the blood and maintain a number of other essential physiologic processes. Kidney diseases, as well as other systemic and metabolic diseases may drastically alter vital kidney functions. When the disease is chronic and progressive, symptoms ultimately evolve in a final pattern of end-stage disease with irreversible kidney failure and its characteristic symptom complex, uremia. The National Institute of Arthritis, Metabolism, and Digestive Diseases is the focal institute at the NIH for kidney research and diseases of the urinary tract.

Obligations for Programs in Kidney Disease and Artificial Kidneys

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, & Digestive Diseases	$18,127,000	17,726,000	21,404,000*	16,729,000	17,592,000
Health Resources Administration:					
Regional medical programs	8,353,000	2,461,000	5,651,000	0	0
Total, PHS	26,479,000	20,187,000	27,055,000	16,729,000	17,592,000

*Includes $2,552,000 in 1974 from restoration of 1973 impounded funds.

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KIDNEY DISEASE AND ARTIFICIAL KIDNEYS

Kidney and urologic diseases are a major area of research of the National Institute of Arthritis, Metabolism, and Digestive Diseases. The Institute supports many fundamental and clinical studies aimed at broadening our understanding of the functions of the kidneys and improving our ability to prevent, control or cure the various kidney diseases through research grants and contracts awarded to medical centers, universities, and industrial and development organizations across the United States. Reports from this research demonstrate that impressive advances in life-saving knowledge and techniques are resulting from this Federal initiative.

KIDNEY DISEASE RESEARCH

The kidney is the central organ in one of the most complex body systems and has the function of maintaining a stable internal environment through removal of the end products of biochemical processes from the blood and regulation of the body's electrolyte composition and fluid and acid-base balance. The kidney also affects other physiological processes, such as regulation of blood pressure and stimulation of the formation of red blood cells.

Many aspects of the kidneys and of the urinary tract are being studied such as: kidney structure as correlated with function, control of sodium excretion, congenital malformations, drug-induced kidney damage, effects of streptococcal host infections and of disorders of immunity on renal tissues, subcellular reactions to injury in the kidney, vitamin metabolism, chronic renal disease, and its complications such as renal osteodystrophy (uremic bone disease).

Three kidney disease groups - infectious, hypersensitive, and hypertensive - account for about three-quarters of all renal deaths. To achieve a reduction in the number of these deaths, better methods of preventive treatment, intensified case-finding and more effective, prompt therapy and, above all, greater understanding of the basic causes and mechanisms of disease are essential. While supportive measures for end-stage kidney disease, such as dialysis or transplantation, are life-saving and life-extending, the most desirable objective of research is, of course, control and prevention.

The Calciuretic Effect of Dietary Protein

Since 1920 several different investigators have observed that the addition of meat or other protein source to the diet causes an increase in urinary calcium in man. In recent research, NIAMDD grantee Dr.

Sheldon Margen and associates at the University of California were the first investigators to use well-controlled formula diets in an attempt to make a critical evaluation of the effect of protein intake on urinary calcium excretion (calciuria).

A markedly positive correlation was found between the amount of protein ingestion and the degree of calciuria. Increasing the daily protein intake from 0 to 90 grams resulted in an approximate 800 percent increase in calcium excretion, irrespective of calcium intake. This effect of protein intake occurred in all the various studies conducted and was also observed with administration of pure L-amino acid mixtures. The data clearly demonstrate that urinary calcium is directly related to protein intake but four other minerals studied (magnesium, sodium, potassium and phosphorus) are not. The investigators report that the mechanism of this calciuretic effect of protein is as yet unclear.

Chronic Kidney Failure

The therapeutic value of administration of keto-analogues of the essential amino acids to patients with chronic renal failure and clarification of the mechanisms by which these compounds act is being studied by Dr. Mackenzie Walser and associates, grantees working at Johns Hopkins University. Goals of the investigations include the exploration of long-term keto-acid therapy in patients with the disease and the development of keto-acids for intravenous use. Thus far, the investigators have established that the keto-analogues of five essential amino acids, valine, leucine, isoleucine,methionine and phenylalanine, when administered along with the four remaining essential amino acids, lysine, threonine, tryptophan and histidine, diminish urea nitrogen appearance and make nitrogen balance more positive or less negative in patients with chronic renal failure. The investigators have also shown that hydroxy-analogues of isoleucine, methionine, and phenylalanine can substitute for the corresponding amino acids in the diet in rats. Since the hydroxy form is more stable, less expensive and more palatable than keto-acids, the investigators have initiated studies with these analogues in patients with chronic renal failure to determine the efficacy of these compounds in reducing urea production and accumulation.

Further benefits of these studies include a better understanding of how nitrogen is transferred between organs and how external nitrogen losses might be modified, which may lead to a better understanding of dietary essential amino acid measurements and to a possibility of reducing the patient's daily protein requirement.

Selective Renal Vein Sampling in Hypertension

Detection of surgically correctable kidney damage has been improved by a study showing that selective renal vein sampling in hypertensive patients with segmental renal lesions can identify and localize such sources of renin. The study was conducted by NIAMDD grantee Dr. Edward G. Biglieri and associates at the University of California.

Renin, a proteolytic enzyme produced by the kidney, is involved intimately in the pathogenesis of an important type of hypertension. Whenever a kidney, or a segment thereof, is deprived of an adequate supply of oxygen, renin is released from the oxygen-starved renal tissue and enters the general circulation where it causes, indirectly, a generalized increase in blood pressure. A comparison of bilateral renal vein renin levels is of value in evaluating hypertensive patients who may have unilateral renal ischemia; sampling of the main renal vein would be of little use, however, in assessing the importance of the occasional lesion which affects only a segment of one kidney.

The investigators recently demonstrated that selective sampling of venous drainage from such isolated lesions is both technically feasible and diagnostically rewarding. They now have shown that selective renal vein renin sampling can specifically identify a localized source of renin that may be overlooked by main renal vein sampling and, thus, can facilitate detection of patients with surgically correctable lesions. The technique should improve the diagnostic value of renin measurements in patients with segmental renal lesions, particularly since remedial surgery can reduce elevated blood pressure in 90 percent of such patients.

Urinary Tract Stones

The study of kidney stone formation is an area which deserves increasing investigative activity, Dr.Charles Y. Pak and associates at the University of Texas Southwestern Medical School postulate that calcium oxalate crystals are critical for the formation of most stones. These investigators are studying the growth and structure of these crystals in different media in the presence of various additives, such as sodium pyrophosphate, sodium tripolyphosphate, magnesium nitrate, creatine, and urea. Their findings indicate that these additives aid the dissolution of calcium oxalate crystals.

In another study, Dr. pak and his associates working with Dr. Frederick C. Bartter of the National Heart and Lung Institute report that they controlled the hypercalciuria and recurrent renal stone disease associated with calcium hyperabsorption by means of a low calcium diet and daily administration of cellulose phosphate. The treatment was well tolerated and no serious side-effects were observed.

Cellulose phosphate is known to have a high affinity for calcium, is nonabsorbable, and is only slightly hydrolyzed in the gastrointestinal tract. The investigators say it apparently acts by binding dietary calcium in the tract, thereby decreasing its absorption into the circulation, and thus its subsequent urinary excretion. Although this blood calcium-lowering effect might stimulate parathyroid hormone (PTH) secretion, neither blood PTH concentrations nor bone density changed significantly during treatment. Moreover, because it is not absorbed, cellulose phosphate administration was not associated with soft-tissue calcification.

This study indicates that, in patients with increased intestinal absorption of calcium, hypercalciuria may be corrected and calcium renal stone formation prevented by a low-calcium diet and decreased intestinal calcium absorption secondary to calcium binding by cellulose phosphate.

Electron Probe Microanalysis

Electron probe microanalysis for analysis of the ionic composition (sodium, potassium, calcium, magnesium, chloride, phosphate and sulfate) of glomerular ultrafiltrate and proximal and distal tubular fluid samples is being applied in a few grantee laboratories conducting investigations of the kidney. The advantages of the system are its specificity for many ions which are presently difficult to identify, the minute (picomolar) samples needed and the preservation of the sample following analysis. With this technique, data may be obtained to give insight into transport mechanisms by comparison of the electrolyte composition of tubular cells to that of tubular fluid content. It is also anticipated that these methods can be applied to the study of processing and locating drugs within the kidney and other organs.

ADVANCES IN KIDNEY TRANSPLANTATION

Several of the National Institutes of Health support research aimed at improving organ transplantation procedures. The NIAMDD has been the principal supporter of research in kidney transplantation. The kidney is the organ most frequently transplanted, and to date over 15,000 kidney transplantations have been performed throughout the world. Depending on the selection of the donor organ and how close donor and recipient tissue types are matched, between 45 and 85 percent of kidney transplants remain functional after two years. Some recipients (a special class: patients who have received kidneys from an identical twin) are now in their second decade since receiving a kidney transplant.

In patients with chronic progressive kidney failure, emergence of the end-stage syndrome of uremia may be delayed by using special diets. Subsequent to this stage, artificial kidneys are widely used and may allow patients to live relatively normal lives. In many cases, a kidney transplant permits a more natural existence, although drug treatment to prevent immunologic rejection of the kidney must be continued indefinitely in all cases except those involving organ transplants between identical twins. Complications from the continued use of immunosuppressive drugs are frequent.

Transplant rejection is an obstacle to the routine use of kidney transplantation, and research continues to focus on the search for drugs that suppress the body's immunologic mechanisms, and on improved immunologic matching of donor kidneys with suitable recipients. Preservation of cadaver kidneys for proper matching with a suitable recipient has improved, and the problems of preserving kidneys for distant recipients have diminished in recent years, although improvements in methods of preservation still are needed.

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Organ Preservation

A cadaver kidney prior to transplantation preserved at 25°C for one hour has less than 25 percent chance of survival due to progressive damage during this period of "warm ischemia." Although drugs such as methylprednisolone and phenoxybenzamine have been used to protect such kidneys, and all such kidneys are now quickly cooled and preserved through cold storage with or without pulsatile perfusion using special supercooled solutions, about one in ten must be discarded because of resultant tissue damage.

Recent research by NIAMDD grantee Dr. John S. Najarian and Dr. Luis H. Toledo-Pereyra of the University of Minnesota has shown that allopurinol, an anti-gout drug, enhances tissue and organ survival during hypoxia. They have shown that allopurinol protects dog kidneys from the deleterious effects of warm ischemia during preservation, and that it may have potential clinical value in organ preservation for transplantation. Based upon their results in animal research, the investigators currently are planning clinical trials of human kidneys.

Matching HL-A Antigens and Transplant Survival

For some time scientists have been investigating the possibility that a patient's chances of success with kidney transplantation can be enhanced by matching of HL-A antigens of his blood with that of the donor. This has been found to be true when the donor and recipient are from the same family, and workers are continuing studies to determine whether such matching significantly improves the survival of kidney transplants between people who are not related. Institute grantee Dr. F. O. Belzer and associates at the University of California, however, recently reported a study in which they analyzed 200 unrelated cadaver kidney grafts and found no correlation between graft survival and degree of closeness of HL-A matching. The investigators state that the results of their study indicate that cadaver kidneys may be transplanted even if the recipients are poorly matched for HL-A antigens.

ARTIFICIAL KIDNEY - CHRONIC UREMIA PROGRAM

It is estimated that about 60,000 patients annually suffer irreversible, fatal kidney failure. This damage may be caused by primary kidney diseases such as glomerulonephritis, by longstanding high blood pressure or kidney infection, kidney stones, advanced diabetes or longstanding and neglected hypertrophy of the prostate gland. Among those who succumb to end-stage kidney disease each year, over 10,000 are considered suitable candidates for maintenance dialysis.

Among those patients who are treated on dialysis, many experience a number of undesirable complications, and the cost of providing this kind of therapy continues to be high. Kidney transplantation is a possible alternative, but many patients cannot withstand major surgery, and even those who do undergo transplantation must be sustained on dialysis until a proper donor organ is located. After surgery the patient may again receive dialysis if the new kidney does not function properly at first or is subsequently rejected. There is one more important function of

artificial kidneys: they are used as a means of life-maintaining support in cases of acute kidney failure, as well as in the treatment of a moribund patient with accidental or suicidal drug over dosage. In these settings the use of dialysis may be decisive in the outcome.

Since its organization in 1966, the goals of the Artificial Kidney - Chronic Uremia Program of the Institute have been to bring about improvements in artificial kidney apparatus and methodologies. Optimal development of new, better dialysis apparatus and methods is still hampered by incomplete knowledge concerning the specific nature of uremic toxicants. For this reason, research into the fundamental aspect of the toxic nature of uremia and basic and clinical studies of the long-term effects of uremia and of dialysis treatment are essential.

About 70 research and development projects are supported by contracts with universities and nonprofit and industrial research laboratories to give a broad approach to problems of highest priority. These include clinical trials of more efficient or less costly dialyzers, development of special adsorbents for uremic toxins, studies to elucidate the nature of the aberrant metabolic changes in uremia, and the maintenance of a national registry of all patients who are being treated with dialysis. The Program is also funding studies aimed at isolation and identification of toxic factors which must be removed from the patient's blood, in addition to metabolic wastes and other substances that accumulate during kidney failure. Many projects are directed at pathophysiology of uremia in an effort to prevent or control complications.

Much has been achieved in the past few years. Clinicians now have an adequate -- though not optimal -- mode of dialysis based on treatment three times each week, usually lasting six hours. Peritoneal dialysis, a method of filtering impurities from the blood utilizing the lining of the abdominal cavity, or peritoneum, and its blood supply as a dialyzing cavity, is at a stage that it can now be utilized for chronic maintenance therapy either in the home or in an institutional setting. Investigators have learned a great deal about how to deal with and possibly avoid osteodystrophy (uremic bone disease) associated with long-term dialysis, but this and other medical complications still pose serious problems.

Research and development in this field must focus on achieving dialytic therapy which would be provided to the patient on a daily basis, or alternate-day basis, for relatively short periods, and which could be self-administered when conditions are suitable. In very preliminary trials, portable dialysis equipment is now being tested which would allow patients to perform their own dialysis treatment away from the home or dialysis centers. A high priority for future improvement involves long-term, well-controlled, multiclinic studies to compare the effects on clinical well-being of short-term daily dialysis and long-term periodic dialysis.

A conspicuous impediment to daily dialysis is the imperfect interface between man and machine which now exists. In some treatment facilities, patients are using a single needle device in conjunction with A-V fistulas (subcutaneous, surgically constructed connections between an artery and a vein) for abbreviated daily dialysis. This may be an important advance toward a better method of coupling the human circulation to an extracorporeal dialyzing device.

Another important goal is to improve dialyzer design so as to lower the hours of dialysis from the accepted 18 hours per week to 10 to 12 hours or less. This can be done by increasing the filtering surface area of dialyzers or through the introduction of more permeable dialysis membranes.

Scientists must also focus on the prevention of known complications of long-term dialysis, namely renal osteodystrophy, anemia, peripheral neuropathy, and premature cardiovascular death. Data from the National Dialysis Registry show that the leading cause of death in long-term dialysis is heart disease followed by strokes. Strong emphasis must be placed on studies of alterations in patterns of fat and carbohydrate metabolism which occur during the course of long-term dialysis since these conditions are suspected of being causally related to premature degenerative changes in blood vessels. Another area where studies must be focused is preventing anemia.

New Ultrafiltration Cell

Scientists at the University of Pennsylvania, supported by a contract from the Artificial Kidney Program, recently developed an ultrafiltration cell to remove excess sodium and water efficiently, rapidly, and inexpensively from fluid-overloaded patients on chronic hemodialysis. The device, which can be used in series with an artificial kidney or as a separate unit, may enable physicians to treat more rapidly and efficiently patients with edema secondary to cardiac failure with acute pulmonary edema. Current treatment of edema, regardless of its cause, employs low-sodium diets and diuretic medication. Treatment usually requires days to weeks, while a few unresponsive patients may require salt and water removal with peritoneal dialysis or the artificial kidney.

In treatment with the new device, arterial blood is delivered to the ultrafilter by a blood pump, filtered and measured and returned to the patient. This therapy is simpler and safer than fluid removal by peritoneal dialysis or hemodialysis. No serious complications, such as clotting (which is prevented through use of an anticoagulant) occurred in over 100 trials. The investigators suggest this therapy could logically be extended to patients with chronic congestive heart failure or pulmonary edema, and would conceivably replace costly and prolonged hospitalization with one or two relatively brief ultrafiltration treatments.

New Prosthetic Arteriovenous Shunt Available

A new implantable, compact prosthetic arteriovenous blood access shunt, developed and tested by Institute grantee Dr. T. J. Buselmeier and associates at the University of Minnesota, has now been made available commercially. The new shunt offers several advantages over standard shunts and passages, notably faster blood flow and less clotting and very few complications. Because of its shorter length and decreased resistance, the device allows three times faster blood flow than the standard Quinton-Scribner shunt. The faster flow prevents blood sludging and clotting, decreases the incidence of infection and trauma, and provides for prolonged shunt survival. The new shunt has been implanted in many patients previously unable to maintain functional standard shunts. Its commercial availability represents an important advance in the technology of hemodialysis.

Clinical Control of Renal Osteodystrophy

Many of the patients maintained with repeated dialysis suffer from uremic osteodystrophy, the characteristic bone demineralization which weakens the skeleton and makes it prone to fractures. In many cases, excess calcium and phosphate liberated from the skeleton may be deposited in soft tissues in the joints, the eye, and even heart muscle. Bone weakening is the end result of a combination of factors. The progressive decrease of kidney function allows excessive phosphate to be retained in the body at the same time that impaired vitamin D activity prevents adequate intestinal absorption of dietary calcium. In an effort to increase calcium blood levels to normal, the parathyroid gland secretes excessive amounts of parathyroid hormone, which in turn causes a mobilization calcium and phosphate from the bone to compensate for low blood calcium of levels.

In research previously reported, an Institute grantee demonstrated that vitamin D is not biologically active in the body, but a tertiary derivative of this vitamin is highly active. Vitamin D is converted in the liver to 25-hydroxy vitamin D3 and then by the kidney to the highly active form - 1,25-dihydroxy vitamin D3 (1,25-DHCC). The actions of the vitamin were evaluated recently by NIAMDD grantee Dr. Anthony W. Norman and associates of the University of California. The investigators studied the biologic response of normal and uremic subjects to 1,25-DHCC, and found that minute quantities produced a substantial increase in intestinal calcium absorption in the normal subjects. Much larger doses were required to augment calcium absorption and correct "vitamin D resistance" in patients with advanced renal failure, observations compatible with defective renal production of the metabolite in such patients. These studies provide support for the opinion that 1,25-DHCC production is impaired in uremic patients. They also furnish insight into normal requirements for the vitamin D metabolite and offer a point of reference for its effects in various disease states.

In other research, Institute grantee Dr. James M. Burnell and associates at the University of Washington performed bone biopsies of normal patients and those with renal osteodystrophy and found evidence that the progression of renal osteodystrophy is associated with decreased

carbonate content in areas of osteomalacic lesions or osteofibrosis. The investigators report that their data appear to identify the existence of a bone "maturational defect" previously found only in rodents. They found a decrease in bone carbonate and an increase in magnesium. The investigators suggest that more research would be necessary to determine whether this may be ascribed to the hyperparathyroidism which characteristically afflicts patients with chronic renal failure.

It has been shown by other investigators that overactivity of the parathyroid gland and calcium abnormalities can be partially avoided in dialyzed patients by restriction of phosphate intake. This is done by adding phosphate-absorbing substances to the diet. It has also been found that elevation of the calcium concentration in the dialysis bath will obtain higher calcium blood levels and counteract the tendency for secondary hyperparathyroidism. A combination of both phosphate restriction and blood calcium increase, if started early enough, has been shown to be effective in preventing the bone dystrophy of chronic renal failure.

Accelerated Atherosclerosis in Prolonged Maintenance Hemodialysis

Evidence has been accumulating in recent years to suggest that cardiovascular disease is the leading cause of death among patients undergoing chronic hemodialysis therapy. Institute grantee Dr. Belding H. Scribner and associates at the University of Washington have obtained evidence in a retrospective study of 39 patients on prolonged hemodialysis that accelerated atherosclerosis is a major risk. The study revealed a mortality rate of 59 percent, with 14 of 23 deaths resulting from atherosclerotic complications; myocardial infarction was responsible for eight deaths, strokes for three, and refractory congestive heart failure for three. The incidence of these complications was many times higher than for non-uremic, normal and hypertensive groups of comparable age, and similar to rates found in Type II hyperlipoproteinemia (an inherited condition of having excess lipoproteins in the blood which characteristically lead to early atherosclerosis and cardio vascular impairment). The data suggest that the probability of dying from such complications increases with time on dialysis, and that dialysis candidates with symptomatic cardiovascular disease probably should not receive chronic hemodialysis. At the same tiem, they note, such life-prolonging therapy cannot be denied by the fear of potential vascular complications, inasmuch as ongoing research may ultimately result in proper control of the etiologic factors involved in accelerated vascular disease.

The Hematologic Effect of Androgen in Uremic Patients

Several NIAMDD grantees have shown in recent studies that the androgenic hormones, testosterone and fluoxymesterone, can improve the anemia associated with chronic renal failure in patients who are on maintenance dialysis. Further studies are needed, however, to determine whether patients without kidneys are as responsive to androgen therapy as are those who have not undergone nephrectomy.

Research by Institute grantee Dr. Walter Fried and his associates at the University of Illinois Medical Center has shown that anemia becomes more severe, and more resistant to androgen (testosterone)

therapy, after the kidneys are removed, as evidenced by packed cell volume and erythropoietin responses. These studies support the clinical impression that nephrectomy should be delayed as long as possible in patients with chronic renal failure who are undergoing maintenance dialysis. The researchers say their findings indicate that androgens stimulate erythropoiesis largely by increasing the amount of erythropoietin produced by kidney remnants even after the excretory function of such remnants has ceased.

Conferences, Publications, and Scientific Communication

Symposia and workshops on critical problems and opportunities in kidney disease research are organized regularly by NIAMDD or co-sponsored with a particular university research center. In 1974, the Institute organized or co-sponsored symposia on the following subjects: 1) Treatment of the diabetic end-stage kidney disease patient, 2) Endocrine functions of the kidney, 3) Adequacy of dialysis treatment (and how to assess and improve it), and 4) Novel therapeutic approaches to uremia. These conferences were attended by several hundred research workers and practitioners in the respective fields. The proceedings were published in prestigious scientific journals and distributed to a readership of several thousand.

Each year, also, the Institute brings together the research contractors of the Artificial Kidney program with staff and consultants for a comprehensive meeting at which all ongoing work is reported and discussed. Extensive illustrated proceedings, describing the most recent advances, are subsequently published and widely distributed to interested research workers and practitioners in the field of dialysis.

For years, the Institute has published, on a quarterly basis, a current-awareness publication, Artificial Kidney Bibliography. This publication provides bibliographic citations of the latest research findings from throughout the world (regardless of language of original publication) in the field of end-stage kidney disease treatment. This very popular publication is now being enlarged into a new, comprehensive publication, Kidney Disease and Nephrology Bibliography which will appear regularly every two months and will cover the entire field of kidney disease and research related to the kidney and urinary tract.

The Institute also distributes to individuals and concerned groups pamphlets descriptive of kidney disease, dialysis, and kidney transplantation, and responds to inquiries on specific related topics.

National Dialysis Registry

Data gathered by the National Dialysis Registry, organized and maintained by the Institute's Artificial Kidney Program, now covers about 85-90 percent of the individuals receiving dialysis treatment in the United States. Since its implementation in mid-1969 the Registry has accumulated data on approximately 16,500 people treated in more than 400 dialysis programs throughout the country. Currently, the Registry data indicate that over 13,000 patients are now being treated by chronic intermittent dialysis. The data currently collected includes that necessary for patient identification and primarily demographic information, including location of the treatment, type of dialysis, age, sex, and reason for discharge

from dialysis treatment. If death is the reason for discharge, the immediate cause of death and underlying conditions are also recorded. Another item of information which the Registry began collecting this year is the clinical diagnosis for kidney failure if it is known, and this information is now available on approximately 3,400 patients.

Registry data on mortality taken from death certificates indicates that heart disease remains the most prevalent primary cause of death. Other data show that since 1970 the dialysis patient population for the country as a whole has grown from 24.4 patients per million population to over 55 per million. This means that the number of persons being treated in dialysis programs has more than doubled over the last four years.

OUTLOOK

Research conducted and supported by the National Institute of Arthritis Metabolism, and Digestive Diseases has contributed much to the understanding and treatment of kidney disease. Now through the recent funding of a study, Evaluation of Research needs in Nephrology and Urology, in which over 90 clinical and basic scientists in the field are participating, the program to reduce kidney disease should gain new impetus. The objectives are to assess current research in kidney and urinary tract disease, define the needs for future research in these areas, evaluate the feasibility of carrying out significant research, establish priorities for approach to the various needs that are identified and to present the results to the scientific and lay community.

PARKINSON'S DISEASE AND TORSION DYSTONIA

Parkinson's disease is one of the most severely crippling chronic disorders of the nervous system. Estimates of prevalence range from one case per 1,000 to one case per 200 population. The disease most frequently attacks people in their 50's and 60's. Parkinson's disease is rarely a primary cause of death, but it often weakens the victim so that he falls prey to other diseases. The National Institutes of Health (NIH) has had a long-standing responsibility for research and research support in parkinsonism, dating from the establishment of the National Institute of Neurological Diseases and Stroke (NINDS) in 1950.

Obligations for Programs in Parkinson's Disease

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health National Institute of Neurological Diseases and Stroke...	$3,339,000	$3,342,000	$4,138,000	$3,158,000	$3,404,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

First described in 1817 by James Parkinson, a London physician, Parkinson's disease affects the brain centers involved in the control and regulation of movement. The intellect, however, is ordinarily unimpaired. Due to disordered control of movement, rigidity of the muscles develops, accompanied by uncontrollable trembling of the extremities, stooped posture, loss of facial expression, and difficulty in walking, talking, writing, or any action requiring a high degree of muscular coordination.

The cause or causes of Parkinson's disease are still unknown. Certain forms may result from a still undetected virus, and a few metallic poisons have been suspected. One theory on the cause is that coordinated muscle control depends upon a balance of two neurochemical systems, cholinergic and dopaminergic, and that the symptoms of parkinsonism arise from overactivity or underactivity of one or the other of these systems. This theory has been strengthened in the past few years by striking advances in drug treatment, which is thought to work by correcting these chemical imbalances. It tells us nothing, however, about what causes the imbalances. Accordingly, the "big push" in research today is in finding out more about the chemistry of the brain and nervous system, and how to manipulate it for human benefit.

Treatment

Treatment in the past consisted of physical therapy to help counteract the muscular rigidity, brain surgery, now used infrequently and effective mainly against tremor, and an array of drugs of very limited effectiveness.

Recent research has shown that depletion of dopamine, a natural substance found in the brain, and necessary for nerve impulse transmission, accompanies parkinsonism. A scientist at Brookhaven National Laboratory, Upton, New York, now an NINDS grantee, in a series of highly successful experiments in the late 1960's, found that it was possible to replace the missing dopamine by a gradual

buildup of large oral doses of its metabolic precursor, an amino acid, levo-dihydroxyphenylalanine, abbreviated as L-Dopa, or levodopa. The treatment benefited two-thirds to three-fourths of all Parkinson patients, and as many as 20 percent were freed of all symptoms. Levodopa has thus been widely acclaimed as the first successful antiparkinsonism drug, and its discovery opened up new hope for patients and research opportunities for scientists.

The new therapy, however, has not been without problems. Chief of these has been the side effects caused by the extremely large doses necessary to control symptoms. Levodopa is broken down very rapidly in the body, and large doses are necessary to achieve the saturation required for penetration into the brain. A way around this problem has been found through the use of enzyme inhibitors, substances which slow the metabolic breakdown of levodopa, allow more time for it to penetrate, and make possible a reduction of dosages by as much as 80 percent. One enzyme inhibitor, carbidopa, has been undergoing trials at NIH and in a number of other medical centers, and is expected to be approved for prescription sale within the next few months.

Unfortunately, even this combination does not solve all of the patient's problems. Adventitious movements (twitching) still occur, some patients experience an "on-off" effect, in which response to the drugs is not uniform, and the drugs do not seem to slow the progression of Parkinson's disease. The drugs represent an enormous advance over the standard treatment of the 1960's, but the battle is far from won. Other drugs are being tried, and hundreds of experiments are contributing to the final answer of the molecular puzzle.

The Research Program

The NINDS research in parkinsonism includes grant support for several large interdisciplinary research groups and approximately 20 smaller, more circumscribed research projects. Also, there is a substantial intramural research program in Bethesda, focused on drug studies. A few persons who cannot benefit from drug therapy are admitted as surgical patients at the NIH Clinical Center.

Mount Sinai. One of the large teams is located at Mount Sinai School of Medicine in New York City. This group, now 12 years old, is continuing a highly productive basic research effort in conjunction with operation of a clinical center for Parkinson patients. Basic studies include a series of projects in neurochemistry and pharmacology, neurophysiology, ultrastructure and histochemistry, nerve regeneration, and neurovirology.

The search for a viral agent in Parkinson's disease was stimulated this year by a report from the Center. For many years physicians have diagnosed some Parkinson patients as having post-encephalitic parkinsonism, believing it to be, in most cases, a long delayed, possibly slow-viral aftereffect of the world-wide influenza pandemic following World War I. No proof of this connection, however, has been found. The Center's finding--that Type A influenza virus antigen had been demonstrated in brain tissue from six patients who had had post-encephalitic parkinsonism, but was absent from the brains of six patients who had had the idiopathic (cause unknown) form, has interested many scientists. As well as providing strong evidence for a viral cause in these cases, the work supports the view that the two forms are distinct.

The Mount Sinai team, which was the earliest to conduct trials with L-Dopa on a large scale, has accumulated a large mass of data on this form of therapy. In a follow-up of a group of 60 patients started on L-Dopa in 1968, the scientists have found no untoward effects from the drug at autopsy in the 18 patients who have died. In this early group they found an average prolongation of life of one and a half years. Quality of life was much improved, though the therapeutic response to L-Dopa was found to decrease somewhat after a few years. Contrary to some reports, they found that intellectual capacity is maintained after long-term treatment. As L-Dopa therapy improves, and more is learned about adjunctive drugs to enhance its effects, the outlook for patients will undoubtedly improve.

One of the problems with levodopa has been the "on-off" effect: wide and rapid variations in response, arising in part from the fact that some patients have a critical serum dopa level below which their symptoms recur. The Center has reported some success in controlling this effect by restricting dietary protein. "On-off" control does not, however, seem to be one of the benefits of combining levodopa with enzyme inhibitors or other drugs.

University of Colorado. In another research center, at the University of Colorado School of Medicine, a broad scale clinical and laboratory investigation of levodopa and catecholamine metabolism is in progress. A large group of patients is being studied over a three-year period. Levels of metabolites are being monitored in sequential urine samples, and correlated with therapeutic and side effects, including psychiatric status. This center has a strong psychiatric interest, and the role of neurotransmitters in schizophrenia is being studied along with their role in organic brain disease. In untreated Parkinson patients, for example, low urinary dopamine excretion correlates with schizophrenic symptoms as well as with Parkinson symptoms. Just as studies in blood pressure lowering agents led to the most effective antiparkinson drug yet found, studies of neurotransmitters in parkinsonism could lead to new approaches to one of the most baffling of the mental disorders.

Brookhaven. At Brookhaven National Laboratory, the group credited with the development of L-Dopa therapy is continuing an extensive biochemical and genetic exploration of parkinsonism. First interested in manganese poisoning, the symptoms of which are similar to those of parkinsonism, the Brookhaven scientists are continuing to search for a role for manganese in neurotransmission.

By feeding manganese to newborn mice they have found that cerebral dopamine levels correspond with cerebral manganese, and feel that this provides strong evidence that the metal participates in the development and normal functioning of the dopamine neurochemical system. As with some other trace metals, minute amounts may be necessary to life, while larger amounts may damage or destroy it.

Also in progress at Brookhaven are studies of novel antiparkinson drugs. In a continuation of work reported last year with apomorphine, the scientists have reported that both this drug and a recently developed analogue, N-propyl-norapomorphine, show promise as an alternative to L-Dopa. In beginning trials of apomorphine in a group of 14 patients, they noted improvements by at least 50 percent in five patients, and lesser improvement in three others. Subsequent trials of the analogue have shown antiparkinson effects at much smaller doses, with some improvement in safety.

National Institutes of Health. Apomorphine is assumed to be a dopamine receptor agonist--a drug which works more directly than levodopa, which must be changed into dopamine in the brain before it can ameliorate symptoms. NINDS scientists are also working with dopamine receptor agonists, and have reported interesting results. In one study, piribedil was given in a single blind crossover trial to 16 patients with parkinsonism. At maximum dose levels, overall improvement averaged 30 percent. While the drug appears to be only about half as effective as the levodopa-carbidopa combination, it offers an alternative for patients who cannot tolerate levodopa, and provides an additional way to study the mechanisms by which drugs modify symptoms.

In parallel with the intense interest in the neurotransmitter, dopamine, from which has come a treatment for parkinsonism, a similar interest has mounted in another transmitter, gamma-aminobutyric acid, abbreviated GABA. This substance has been found to be depleted in the brain tissues of patients with Huntington's chorea, a disorder similar in some respects to parkinsonism, and affecting the same areas of the brain. However, like dopamine, GABA does not usually cross the blood-brain barrier, a protective biochemical screen, and it often produces undesirable side effects. An intense search is underway for a means of replacing

the GABA as a possible treatment for Huntington's chorea, and if the search is successful, much more of the whole mechanism of all the movement disorders, including parkinsonism, will be laid open to scrutiny. The NINDS intramural activity is one of the leading efforts in this area of neuropharmacology.

Trials of several other drugs were reported during the year. Fusaric acid, an inhibitor of an enzyme leading to formation of norepinephrine (which stimulates motor activity) was tried in 15 patients with parkinsonism. The drug failed to alter the severity of symptoms in otherwise untreated patients, or to exert any effect in levodopa-treated patients.

In another study, two complex substances produced by cells in the hypothalamus, a control center within the brain, were tried: thyrotrophin-releasing hormone, and melanocyte-stimulating hormone release-inhibiting factor (MIF). Although both had been found to have pharmacologic effects in animals, the results were either negative or insignificant in humans. These examples illustrate the enormously difficult tasks facing scientists in their efforts to understand brain function on a molecular level, and to find corrective drugs.

A rare form of parkinsonism, parkinsonism-dementia, or PD, occurs among the Chamorro people of Guam and the other Mariana Islands at a far greater rate than that of parkinsonism elsewhere in the world. It accounts for 10 percent of adult Chamorro deaths, and is rapidly progressive, leading to death in four to five years.

In an attempt to learn why PD is so devastating within this small, isolated population, NINDS operates a permanent research center on Guam where patients are treated and studied. The search is focused on discovering possible genetic or familial factors, and also on uncovering any possible viral or toxic metal causes. Treatment of these patients with levodopa-carbidopa has been highly successful in alleviating the Parkinson symptoms, although the dementia of PD has not been alleviated. In a study reported this year, 10 patients were treated for varying periods. Compared with previous trials using levodopa alone, the combined therapy shortened the time needed for the drugs to take effect, greatly reduced gastrointestinal side effects, and allowed easier control of other disorders. The scientists expect in the near future to have enough experience to determine whether the drugs alter the natural history of this form of parkinsonism, or produce any changes in the morbidity and mortality patterns.

These and other patients in Guam have formed an important resource population for basic studies by NIH scientists. The Guam research center also serves as the setting for cooperative studies which bring in researchers from universities and other institutions.

Outlook

Although great advances have been made in treatment of symptoms, the causes and methods of prevention and cure of Parkinson's disease remain essentially unknown. However, research is steadily progressing, and should soon produce answers to these most critical questions. The gains made in the past five years have justified an optimistic attitude among scientists, physicians, and patients that control of this disabling disease can be achieved.

5
TORSION DYSTONIA

Since its founding in 1950, the National Institute of Neurological Diseases and Stroke (NINDS) has been deeply committed to conquering dystonia. In 1970 the NINDS sponsored a conference on dystonia at which important information regarding the clinical, genetic, pathological, biochemical, and therapeutic aspects were discussed and later published for use by the medical and scientific community. Because of the resulting increase in scientific interest an International Symposium on Dystonia is planned for 1975. NINDS is participating in the Symposium, to which researchers from Russia, Israel, Japan, and a number of other countries have been invited.

Torsion dystonia, or dystonia musculorum deformans, is a prolonged and often incapacitating neurological disorder causing bizarre involuntary movements in its victim's arms, legs, head, and torso. If these movements continue over an extended period of time, they can produce distorted posture.

Prior to 1966 many physicians believed that torsion dystonia was not an organic disorder but rather a functional disorder with a neurotic or hysterical basis for the abnormal movements. That year, findings of NINDS scientists indicated that torsion dystonia was indeed of organic origin. In addition, they were able to identify two hereditary forms. It is now known that there is also an acquired form.

The "recessively inherited" form occurs in about one-fourth of the offspring of parents who carry but do not express the defective gene. The disorder affects primarily people of Eastern European Jewish ancestry. About one out of every 100 Americans of this origin carries the dystonia gene, a frequency only slightly less than the frequency of Tay-Sachs disease. However, because Tay-Sachs disease leads to early death and dystonia usually does not, there are more living patients suffering from dystonia than from Tay-Sachs disease.

The "dominantly inherited" form of dystonia is passed from a parent who usually is affected with the disorder. In one of the many such families under study by NINDS, there are at least 13 affected in 4 generations.

"Acquired dystonia" can result from environmental causes such as head injury at birth, infection, and even certain drugs. There are thousands of patients with this type. Dystonic movements also occur in many patients with other neurologic disorders, including some patients with Parkinson's disease receiving L-Dopa therapy.

At the NINDS, where a registry of hereditary dystonia cases is maintained, 180 affected families involving approximately 500 cases have been evalutated. Many more cases are known but have not been studied. In addition, a special kind of dystonia localized to the neck is relatively common. This condition, which is called torticollis, produces a twisting of the neck and an unnatural position of the head.

At present, NIH research directly devoted to this rare disease includes two genetic and epidemiological studies funded at $35,000, and two other research projects funded at $178,000. A substantial amount of basic, non-categorical research in physiology, biochemistry, and other disciplines is of potential relevance to dystonia, also.

Search for a Cause

The cause of dystonia remains unknown, but many scientists believe the problem originates in an area of the brain called the basal ganglia.

In recent studies NINDS scientists, collaborating with others, uncovered what appears to be a biochemical defect in one form of dystonia involving the elevation of a particular enzyme in the blood of these patients. If this finding is confirmed, it may lead to a better understanding of the nature of these disorders and help to identify victims whose symptoms have not yet appeared. Such a diagnostic tool would be a valuable aid to physicians providing genetic and family counseling.

Advances in Treatment

As yet there is no established treatment for the underlying disorder, but dystonic symptoms can sometimes be controlled by drugs such as diazepam (Valium) which relaxes the muscles. Another drug, L-Dopa, which can cause dystonic symptoms in some Parkinson patients, ironically can help alleviate symptoms in some patients with dystonia. Fortunately the search for effective drugs is becoming much more active.

During 1974 scientists at Mount Sinai Hospital in New York City reported that they have been able to treat dystonia patients successfully with carbamazapine (Tegretol), a drug recently made available for general use following extensive NINDS-sponsored studies. Several dozen patients with both acquired and hereditary forms who were treated with the drug have had sustained improvement for periods up to one year according to the scientists.

Advanced dystonia may be helped by surgery on a structure deep within the brain called the thalamus which influences the body's pattern of movements. Most persons undergoing this operation have been helped at least temporarily. NINDS scientists are continuing their efforts to improve surgical treatment and to develop more effective drugs.

SICKLE CELL DISEASE

Sickle cell anemia is a hereditary blood disorder characterized by the presence of chronic anemia, jaundice, recurrent bouts of pain called "crises," occasional growth retardation, increased susceptibility to certain infections, and occasionally a shortened life span. This blood disorder occurs as a result of the presence of genes for sickle cell hemoglobin inherited from both parents. The incidence of sickle cell anemia in Blacks in the United States is approximately one in six hundred. Some 50,000 or more black persons are affected.

Sickle cell trait is a healthy state wherein an individual carries genes for both sickle hemoglobin and normal hemoglobin. Rarely are there problems associated with the trait. Persons with the trait seldom are aware of it unless they are tested. The trait occurs in approximately one in every ten Blacks in this country or in about 2,000,000 persons.

To date there is no cure for sickle cell anemia. The genetic abnormality in the red blood cells cannot be reversed. Treatment, however, is being improved constantly. Pain-killing drugs, fluids, blood transfusions, proper nutrition and hygiene, bed rest, and protection against acute infections and other stressful factors that bring on crises are being used. Current methods of treatment may make it possible to alter the sickling process, thereby shortening or even preventing the sickle cell crisis and the resulting tissue damage. These must undergo further development and evaluation before their full potential can be realized.

The Department of Health, Education and Welfare's (HEW) activities relating to sickle cell disease are centered in the National Institutes of Health (NIH) for research and in the Health Services Administration (HSA) for demonstration service activities. The NIH serves as lead agency for the coordination of the overall HEW sickle cell program and funds for the program are located in the National Heart and Lung Institute budget. The NIH's research activities in sickle cell disease are primarily the responsibility of the National Heart and Lung Institute. The National Institutes of Arthritis, Metabolism, and Digestive Diseases, and the National Institute of General Medical Sciences also support research in this disorder. The HSA service activities are directed by its Sickle Cell Disease Office, which manages a demonstration service delivery program.

Obligations for Programs in Sickle Cell Disease

	1972	1973	1974	1975 Estimate	1976 Estimate
National Institutes of Health:					
National Heart and Lung Institute...	$10,192,000	$15,320,000	$16,115,000	$16,000,000	$16,000,000
National Institute of Arthritis, Metabolism and Digestive Diseases.....	964,000	1,120,000	1,335,000*	1,070,000	1,016,000
National Institute of General Medical Sciences.....	100,000	100,000	100,000	100,000	100,000
Total, National Institutes of Health	11,256,000	16,540,000	17,550,000	17,170,000	17,116,000

* Includes $135,000 in 1974 from restoration of 1973 impounded funds.

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

In February, 1971, the President's Health Message to Congress highlighted the problem of sickle cell anemia. The message noted that sickle cell anemia is an important health problem and included an additional $5 million in the President's budget for research and service in this hereditary blood disorder. This allowance was later increased to $10 million for research and service activities in sickle cell anemia in FY 72, $15 million in FY 73, $16 million in FY 74, and an estimated $16 million in FY 75.

Subsequent to the President's initiative, the Secretary of HEW named the National Sickle Cell Disease Advisory Committee. The Advisory Committee recommended that the earmarked funds for the National Sickle Cell Disease Program (NSCDP) should be divided proportionately between research and demonstration service activities.

The objectives of the National Program as further recommended by the Advisory Committee are reductions of sickness and death from sickle cell anemia through research and development, both at the fundamental and clinical level; initiation and expansion of community education, screening and counseling; education of medical and allied health professions; broadening of monetary support through federal, state, local and nongovernment participation; strengthening and expansion of the base of black professional and technical personnel; and improvement of clinical care for victims.

A program was developed to implement these goals and objectives. Sickle cell activities for the NSCDP are being carried out by the National Institutes of Health, the Health Services Administration and the Center for Disease Control. Funds for supporting these activities come from the NHLI budget. The Chief, Sickle Cell Disease Branch, National Heart and Lung Institute, NIH, serves as the Coordinator, National Sickle Cell Disease Program. NIH serves as the lead agency for the National Program, with activities of the other agencies supported through reimbursable agreements.

National Sickle Cell Anemia Control Act (P.L. 92-294)

In May 1972, Congress passed and the President signed the National Sickle Cell Anemia Control Act. The purpose of this Act is to establish a program for the diagnosis, control, treatment of, and research in sickle cell anemia.

Specific findings and declarations leading to the passage of the Act were:

1. that sickle cell anemia is a debilitating, inheritable disease that afflicts approximately two million American citizens and has been largely neglected;

2. that the disease is a deadly and tragic burden which is likely to strike one-fourth of the children born to parents who both bear the sickle cell trait;

3. that efforts to prevent sickle cell anemia must be directed toward increased research in the cause and treatment of the disease, and the education, screening, and counseling of carriers of the sickle cell trait;

4. that simple and inexpensive screening tests have been devised which will identify those who have the disease or carry the trait;

5. that programs to control sickle cell anemia must be based entirely upon the voluntary cooperation of the individuals involved; and

6. that the attainment of better methods of control, diagnosis, and treatment of sickle cell anemia deserves the highest priority.

Through the Sickle Cell Disease Branch, NHLI, in cooperation with the Sickle Cell Disease Office, Bureau of Community Health Services, HSA, and the Hematology Section, CDC, several program components have been developed, including Comprehensive Sickle Cell Centers, Screening and Education Clinics, Mission Oriented Research and Development, Biomedical Research, Public and Professional Education, and Hemoglobinopathy Training.

Comprehensive Sickle Cell Centers

Comprehensive Sickle Cell Centers administered by the Sickle Cell Disease Branch bring together research (basic, clinical, clinical trials, clinical application, training) and community demonstration service (education, testing, and counseling). These Centers focus resources, facilities and manpower in a coordinated approach to sickle cell disease, bridge the gap between scientific inquiry and service, and bring findings in one area into practical use in the other. In this way research findings are most efficiently incorporated into the health care delivery system.

Ten Centers were established in FY 1972 and five Centers were established in FY 73. Of the total funds allocated to Comprehensive Sickle Cell Center Programs approximately 40 percent was utilized to support research activities and 60 percent was expended in service programs. Research findings in these Centers include development of methodology for the accurate identification of sickle hemoglobin and other abnormal hemoglobins in samples taken from the umbilical cord at the time of birth. This methodology is highly specific and identifies the hemoglobin pattern possessed by the newborn in spite of the presence of large amounts of maternal blood and fetal hemoglobin. This is the earliest point in the life of an individual that such diagnosis can be made and is highly desirable not only for the early diagnosis but utilizes blood from the unbilical cord which presents no hazard either to the mother or to the newborn infant. Studies have led to the isolation of apparently biologically active messenger ribonucleic acid (RNA) from bone marrow and peripheral cells in patients with beta thalassemia (a disease caused by an abnormality of the hemoglobin which is quite distinct from sickle cell disease). In some cases this abnormality is linked with abnormal AS Hemoglobin (sickle trait) to produce sickle cell-beta thalassemia and the messenger RNA is also of significance in sickle anemia. Of the more than 200 abnormal hemoglobin types which have been identified, most are benign and cause no symptomology in the person possessing them, however in some cases they may be combined with other abnormal hemoglobins producing a significant level of disease. Studies have also suggested that membrane change in the red blood cells of patients with sickle cell anemia is related to the depletion of adenosine triphosphate (ATP), calcium accumulation and defects altering the permeability and passage of different materials through the red cell membrane. Highly sophisticated investigation in physics and chemistry have led to studies in the area of nuclear magnetic resonance (NMR) which are intended to determine the physical and chemical structure and conformation of sickle hemoglobin and any alterations which might be reproduced by chemicals which might reverse the sickling action or deformation of red cells containing sickle hemoglobin. Several studies of the eyes and kidneys in patients with sickle cell anemia and sickle cell variance are in progress to better identify and evaluate abnormalities of the retina and kidneys. Other studies have revealed significant differences in the immunologic reaction in patients with sickle cell disease to various infections when compared to normal controls. It is felt that this difference in reaction is probably related to components found in the serum of the blood.

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The educational programs being conducted in the Comprehensive Sickle Cell Centers have proven highly effective and have resulted in developing a wide range of specialized educational materials, seminars, and lectures directed toward increasing the awareness and knowledge of the general public, high school students, and medical students, interns, residents, and practicing physicians with special attention to socio-economic and ethnic considerations.

All Centers have participated in a proficiency testing program which has resulted in an unprecedented degree of accuracy in definitive diagnosis of all hemoglobin types. Many of these Centers now serve as reference laboratories for positive identification of those samples too difficult to diagnose in other local laboratories. In addition, some of these laboratories have engaged in retesting persons previously diagnosed and have contributed significantly to a more complete diagnosis of hemoglobin patterns, adding to patient satisfaction and peace of mind, and contributing to the overall fund of scientific information related to this field. Counseling programs within the Centers have been developed so as to most effectively communicate with the subject population utilizing vocabulary, illustrations and discussion techniques most acceptable to the individual being counseled. This vital component of interactivities is made available to all persons found to have any abnormal hemoglobin with specific emphasis on sickle cell anemia and sickle cell variants which represent interaction of sickle hemoglobin with other abnormal hemoglobins. Counseling is of a non-directive nature and is in effect a continuation of the educational program provided to the individual prior to testing. During these sessions, accurate definitive information related to the specific case is provided to the individual and assistance may be given in the interpretation of this information. However, decisions respecting the information given must be made by the individual himself with no direction or influence, even of a covert nature, given by the counselor. This procedure results in a high degree of acceptability of these programs and participation by the subject population and in many cases leads to stimulation of community interest because of the gratifying effect from direct honest discussion with mutual respect between the counselor and the person being counseled.

Screening and Education Clinics

Screening and Education Clinics are administered by the Sickle Cell Disease Office in the Health Services Administration. This component serves as a model to determine effective methods of carrying out service activities such as stimulation of public awareness, education, screening, counseling and patient referral under various circumstances and in urban, suburban and rural environments. Twenty-six clinics were supported in FY 74.

Mission Oriented Research and Development

Sickle cell anemia is an hereditary disorder characterized by the presence of painful "crises" which may last for hours or days, a chronic anemia, related to accelerated destruction of red blood cells, and acute or chronic damage to various organs. All these clinical manifestations follow upon the presence of an abnormal hemoglobin (HbS) which aggregates within the deoxygenated red blood cell, leading to a crescentic "sickle" shape of the cell known as the "sickling phenomenon." On oxygenation such sickled cells will usually resume their normal shape. Sickled red cells lose the deformability of normal cells and are unable to traverse the small blood vessels. Occlusion of small vessels by sickled cells lead to the painful crises, which are manifestations of small areas of damage to tissues as a result of impaired circulation. Sickle cells also have shortened survival in the circulation - hence the anemia, and the specific organ damage results acutely from the progressive occlusion of larger vessels, or chronically from repeated episodes of occlusion of smaller vessels.

Targeted research to answer specific questions in sickle cell disease is supported under contracts. Much of the program is based upon the concept that if sickling of the red cells could be impaired or prevented, perhaps by a suitably designed pharmacologic agent, both the quality and duration of life for patients with sickle cell disease would be markedly improved. Twenty-two contracts were supported in FY 75 to study the molecular, cellular, and clinical manifestations of sickling.

Notable accomplishments during the past year include the finding that of all the drugs being investigated, sodium cyanate has considerable promise in therapy. The drug has now been subjected to clinical trials which indicate that a daily dose administered orally to some patients with sickle cell disease achieved a sustained improvement in the degree of anemia and perhaps an amelioration in the frequency of crises. However, its full range of dose-dependent side-effects, specifically neurotoxic effects is not yet known. Preliminary reports of extracorporeal treatment of red blood cells with sodium cyanate suggest that similar improvement in anemia and in frequency of crises can be induced. Thus far, neurotoxic effects have not been observed in patients on extracorporeal treatment. Extracorporeal treatment is that procedure by which portions of blood are withdrawn from the patient and treated outside of the body with sodium cyanate, then reinfused into the patient. Although this technique is cumbersome, it should be explored further.

Studies are in progress to identify cyanate induced morphological alteration in the nervous system of monkeys. This animal model will increase our knowledge as to the efficacy of cyanate for the alleviation of the painful crisis of sickle cell anemia. However, it should be emphasized that careful clinical observations of all patients receiving experimental drugs are mandatory since no animal model is identical to man.

Agents which have been shown to impair sickling include zinc, nitrogen mustard, and alkylureas dimethyl adipimidate. These agents remain to be tested clinically.

In other areas of progress, a test for screening HbS by a "shake method" has been developed. The test is based on the fact that Oxyhemoglobin S in solution precipitates upon vigorous shaking of the solution. This is a simple rapid test which may be used to confirm the presence of sickle hemoglobin or to establish the diagnosis of sickling disorders rapidly in the clinic or at the bedside.

In the area of early diagnosis of sickle cell anemia, methodologies to identify hemoglobin types in single cells obtained during early pregnancy are being developed. Success in this area would allow for positive identification of several abnormal hemoglobins in pregnancy.

A National Symposium on Sickle Cell Disease was held late in FY 74 to permit investigators to describe research over the past two years. Evaluation of the papers will aid in defining promising avenues of research for consideration of support.

Biomedical Research Program

The National Sickle Cell Disease Program conducts a program of investigator-initiated research supported by grants. Forty-nine grants are presently being supported directly. Two program project grants are also administered. These investigations include studies of the basic structure of sickle hemoglobins, methods of altering the abnormal structure, the synthesis of hemoglobin structure, improved detection of abnormal hemoglobins and flow patterns exhibited by cells containing sickle hemoglobin.

Education Program

Education of the public, including health providers and health educators, about sickle cell has received priority during the past year. In addition to continuing education programs by centers and clinics, efforts have been increased to provide factual information through films, lectures, workshops, seminars, tutorial conferences, pamphlets, and brochures. A communication plan was developed with direction and guidance by community organizations and agencies. Emphasis on the comprehensive approach was increased through input by psychologists and social workers. Laboratory personnel have also increased their knowledge through the hemoglobinopathy workshops conducted by the Center for Disease Control (CDC).

To broaden the approach, the program has issued a request for proposals (RFP) to aid in the dissemination of factual information to the public and to conduct educational activities throughout the country. Award of this contract is expected in FY 75.

The increased effort is expected to result in increased public awareness and a better educated community.

Hemoglobinopathy Detection Training Program

Through an interagency agreement, the Center for Disease Control trains personnel of projects funded under the Federal Sickle Cell Disease Program and other laboratory personnel in the detection of abnormal hemoglobins. A proficiency testing program was developed to insure quality control of laboratory techniques in the federally funded screening projects.

Related Activities of Other NIH Institutes

The National Institute of Arthritis, Metabolism and Digestive Diseases is supporting research to develop a sensitive detection technique for identifying sickle cell hemoglobin in a 15-week-old fetus. The procedure should permit early genetic counseling, and ultimately, prenatal diagnosis of sickle cell disease as well as other hereditary disorders of hemoglobin, including thalassemia. Considerably more information will be required before these methods can become generally available.

The National Institute of General Medical Sciences is supporting research in the genetic aspects of sickle cell disease, including the exact genetic alteration which causes the abnormality in the amino acid sequences of the hemoglobin molecule, resulting in the sickling phenomenon.

It is expected that the support of research in sickle cell disease and sickle cell disease-related projects by these other NIH Institutes will continue in FY 75 at a total funding level of approximately one million dollars.

SPINAL CORD INJURY

Severance or other acute injury of the spinal cord is a calamity of the greatest magnitude, devastating to the victim and his family from both the physical and psychological point of view. Once transection of the spinal cord occurs, incapacitation is permanent since restoration of spinal cord function in humans is unknown. The injured person becomes paraplegic, quadriplegic, or partially paralyzed and is condemned to a lifetime in bed or wheelchair. With proper care and rehabilitation, however, many patients can be returned to useful, productive lives.

Today there are an estimated 125,000 paraplegic and quadriplegic patients in the U.S., and insurance figures indicate there are 10,000 to 12,000 new civilian paraplegics each year. Eighty-four percent of the victims are young men between the ages of 18 and 25. Approximately 56 percent of these are injured in automobile or motorcycle accidents, the remainder in sporting or industrial accidents, or gunshot wounds or falls.

By estimate of the Armed Forces the cost of immediate and lifetime care of a paraplegic is $900,000. Indirect costs in terms of lost earning capacity for the individual and reduced productivity for the nation bring the total cost of spinal cord injury to billions of dollars each year. The toll in personal tragedy is incalculable.

The Department of Health, Education, and Welfare's responsibility for programs in Spinal Cord Injury is centered in the National Institute of Neurological Diseases and Stroke of the National Institutes of Health for research and in the Social and Rehabilitation Service and the Office of Maternal and Child Health of the Health Services Administration for service.

Obligations for Programs in Spinal Cord Injury

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health: National Institute of Neurological Diseases and Stroke..	$4,665,000	$5,613,000	$6,309,000	$6,555,000	$6,746,000
Health Services Administration: Maternal and Child Health.....	1/	1/	1/	1/	1/
Total.....	4,665,000	5,613,000	6,309,000	6,555,000	6,746,000

1/ Obligations not identifiable.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

The spinal cord is a bundle of nerve fibers and cells measuring on the average 17 inches in length, and providing the central connection between the brain and the muscles, skin, and internal organs. The cord is enclosed by 7 cervical (neck), 12 thoracic (breast), and 5 lumbar (back) circular blocklike bones called vertebrae. These vertebrae allow a remarkable range of motion while normally protecting the spinal cord and nerve roots from injury. Nevertheless, injury can and does occur.

Causes of Spinal Cord Injury

Direct injuries to the spinal cord may result from falls on the back, industrial accidents, jumping from heights, local stab wounds, gun shot, shrapnel, and other penetrating missiles, and fracture or fracture dislocation of the vertebral bodies. Fractures, however, have long range serious consequences only when injury to the bony spine affects the spinal cord or roots. In other words, a person can have a "broken back" without a spinal cord injury.

Indirect injury to the spinal cord, however, is the more frequent cause of trauma. This may occur as a result of excessive flexion or extension of the spine in falls, diving, and automobile accidents. For example, if a car is struck from behind, the passenger's head may be whipped back. If the vehicle stops abruptly, he may be jack-knifed forward. In a sudden fall the head may strike in a position that flexes the neck acutely, as in a football injury or a slip on an icy pavement. Hyperflexion of the spine is the most common mechanism of spinal cord injury, and is occasionally produced without external force during spontaneous or induced convulsive seizure.

Types of Spinal Cord Injury

The most common injuries to the spinal cord occur from: (1) simple concussion without direct trauma to the cord; (2) compression, contusion, or laceration of the cord substance by penetrating missiles or by fracture dislocation; (3) hemorrhage into its substance; and (4) compression of its blood vessel supply. Among civilians injuries to the spinal cord occur most often at the level of the fifth and sixth cervical vertebrae (vertebrae of the neck) and the eleventh and twelfth thoracic vertebrae (vertebrae of the chest and ribs).

Severity of Spinal Cord Injury

The central part of the spinal cord is soft and easily bruised or squeezed by pressure from surrounding bones. Consequently, cord damage can and does occur above or below the level of bone injury, sometimes without damage to the bony spine itself. It is the level of the injury to the cord, not the level of bone injury, that determines the gravity of the damage. The lower the injury on the spinal cord, the better the outlook for the patient, because more of the cord remains operationally connected to the brain. Once the shock to the cord wears off, muscles controlled by nerves from the spinal cord above the injury often regain full function.

When the injury is in the upper cervical cord, however, immediate prognosis for life is poor because of the frequent development of respiratory paralysis. Lesions below the fifth cervical vertebra are rarely life-threatening for the period immediately following the injury if other bodily organs are undamaged. Death may follow after a period of weeks or months, however, as a result of complications associated with bed sores or bladder dysfunction.

The extent of cord injury is another key factor in assessing recovery. A completely severed cord, as from a bullet or penetrating missile fragment, cannot be repaired, and such an injury always results in permanent motor paralysis and sensory loss below the level of transection.

Among persons who survive spinal cord injury, some degree of improvement is to be expected in all cases except those in which the cord is transected. The outlook is even more optimistic when the symptoms result mainly from contusion or hemorrhage into the cord. As long as some nerve fibers in the spinal cord are uninjured, improvement may occur, usually during the first six months, but sometimes even longer after injury.

Management of Spinal Cord Injury

In the past 30 years, considerable progress has been made in the initial handling, management, and rehabilitation of the spinal cord injured. With growing recognition of the value of comprehensive treatment and care, specialists in physical medicine, neurosurgery, urology, and plastic and reconstructive surgery combine efforts to provide the paraplegic with nursing care, nutritional management, antibiotic therapy, and good medical and surgical treatment. As a result, more and more paraplegics are being socially rehabilitated and returned to useful employment. Sophisticated mechanical aids for walking, including a new pneumatic brace, special devices for operating automobiles, telescoping mouth rods for people without the use of their arms, and removal of architectural barriers to mobility also are improving the outlook for paraplegics. Most encouraging of all, new knowledge, new techniques, and new efforts in regeneration research suggest that as of today the problem of restoring useful function in the damaged spinal cord, while difficult and challenging, should no longer be considered insoluble.

Spinal Cord Injury Research Program

The National Institute of Neurological Diseases and Stroke (NINDS) is concerned with four aspects of the problem of paraplegia: (1) treatment of acute spinal cord injury especially when the cord is not completely severed; (2) development of electrical prosthetic "by-passes" of the injured cord and a neural prosthesis for control of urinary bladder action; (3) use of angiography and evoked response studies in the diagnosis and treatment of spinal cord injury; and (4) research on regeneration of the spinal cord.

The Institute also is supporting a study to provide more reliable estimates of the incidence, prevalence, and costs of spinal cord injuries. In addition, the creation of a spinal cord injury registry will help in planning and providing effective prevention and treatment.

New Approaches to Acute Injury

Recent evidence indicates that the first few hours after spinal cord injury are critical if progression of spinal cord degeneration is to be halted. This has spurred a search for new methods of diagnosis, evaluation, and treatment.

Already some investigators have modified paraplegia in animals by the use of hypothermia (cooling), corticosteriod drugs, and the blocking of norepinephrine production by injections of alpha methyl tyrosine. (Norepinephrine is one of a group of compounds known as catecholamines which cause constriction of blood vessels in the spinal cord.)

These techniques are designed to preserve or restore adequate circulation and thus provide support for the traumatized area to minimize secondary damage.

To exploit these new developments, the NINDS established in 1971, a targeted research program on acute spinal cord injury. The Institute is now supporting Acute Spinal Cord Injury Clinical Research Centers at Ohio State University, Yale University, St. Joseph's Hospital and Medical Center, Phoenix, Arizona, the Medical University of South Carolina, and New York University, and a large project at the University of North Carolina, where multidisciplinary basic research is being pursued.

The centers also have a responsibility for community research on problems such as roadside diagnosis and emergency therapy, rapid transportation to the centers, emergency room differential diagnosis, and patient handling. Proper handling during these phases of injury may well prevent lasting damage to the spinal cord.

In addition, targeted research is supported at Washington University, St. Louis, Hahnemann Medical College, Philadelphia, and the University of North Carolina.

Scientists in these programs are conducting animal studies to assess the effects of agents with a potential for preventing acute tissue change that can lead to complete experimental transection of the spinal cord.

A scientist at Hahnemann Medical College has demonstrated in animals that hemorrhagic damage in the spinal cord may be reduced or prevented by injecting alpha methyl tyrosine, a chemical that interferes with synthesis of the catecholamine norepinephrine.

This finding generated the hypothesis that catecholamines are involved in the production of some cord abnormalities resulting from trauma. Although other investigators have not always been able to confirm this observation, it provides new approaches to regulation of cord microcirculation, and the fundamental role of catecholamines.

The NINDS supports many studies at the molecular and cellular levels. The aim of these is to clarify the processes responsible for spinal shock, pain, and altered sensation. Their goal is to improve treatment.

In furtherance of this, directors of the Clinical Research Centers held a workshop last year and agreed to correlate and standardize an experimental model of spinal cord injury and to establish more efficient ways to collect, store, and retrieve data on experimental studies as well as from human patients. Exchange of information will be continued in future workshops.

It also is anticipated that valuable data will soon be available from the National Spinal Cord Injury Registry, recently started by the Department of Defense. Nine hundred neurosurgeons in the U.S. and Canada are cooperating in this effort by sending the Registry protocol summaries on patients under their care.

Neural Prosthesis Program

Because the muscles of paraplegics are usually intact, it is theoretically possible to activate them in a coordinated manner by electrical signals derived from the brain or from the muscles of the unparalyzed part of the body. This so-called electrical "by-pass" approach is being pursued in the NINDS Laboratory of Neural Control. This laboratory is studying the cells in the brain and spinal cord which control the muscles with the aim of effectively by-passing injuries of the spinal cord.

Another effort applies recent advances in basic neuroscience, engineering, and physical sciences to the development of prostheses. A feasibility study of functional neurostimulation is being carried out through a contract with Case

Western Reserve University. Investigators have implanted intramuscular electrodes in paralyzed patients and are studying the degree of proportional control that can be achieved. Sequential stimulation through multiple electrodes provides graded muscle contractions and reduces fatigue. With a forearm device utilizing electronic controls, patients are able to grasp and use objects such as pencils, cups, combs, and eating utensils.

The Laboratory of Neural Control also has contracts for developing a prosthetic device for bladder control at Duke University, and the University of California at San Francisco. Scientists at these institutions are working with animals to determine if cells in the cord can be selectively stimulated to cause simultaneous bladder contraction and relaxation of the sphincters. Paralysis of the bladder is a principal problem of paraplegics. About fifty percent of all paraplegics face the threat of premature death from kidney infection. Additional studies on effective ways to control the urinary bladder and large bowel are supported by research grants.

Angiography of Acute Spinal Cord Injury

Selective angiographic studies of the spinal cord have been carried out by NINDS neuroradiologists for several years. (Angiography is the process of taking X-ray pictures of blood vessels after first injecting a radioopaque substance). They have developed techniques of visualizing the cord blood vessels for reliable diagnosis in cases of blood vessel malformations.

The use of these techniques has been expanded to patients with other spinal cord malformations, such as tumors and secondary dilations of the blood vessels.

Using this technique, the scientists have visualized vessels of the cord in six patients with acute cervical spine injury. Although the angiographic findings probably did not change the final outcome, they did affect treatment in three cases. In one patient, a decision not to operate was made that proved to be the correct course. In two other patients, the angiography helped determine the type of surgical approach.

Neuroradiologists believe that angiographic observations will undoubtedly assist in the treatment of spinal cord injured patients.

Computerized axial tomography (CAT) by means of the British-developed EMI-Scanner is a new radiographic technique which permits cerebral pictorial analysis. Image reconstruction is obtained from multiple X-ray transmission through the skull processed by computerization. Though introduced only about three years ago, CAT is already having a tremendous impact on the management of many types of brain injuries. This equipment cannot be used in evaluation of other parts of the body, however.

A modified X-ray scanner, the Automatic Computerized Transverse Axial Scanner (ACTA-Scanner), developed at Georgetown University, is able to scan soft tissues everywhere in the body, including the cervical spine and cervical cord. In preliminary studies with the prototype ACTA-Scanner scientists have already been able to obtain useful diagnostic information.

Fortunately, use of this technique will not be limited to the diagnostic studies, but will extend, at least indirectly, to general patient care and affect some economic aspects as well. Risk-laden, technically complex, and costly diagnostic procedures, sometimes requiring lengthy hospitalization, will in some cases be eliminated. The simple, innocuous and noninvasive scanning can often be performed on an outpatient basis. According to an NINDS neuroradiologist, useful diagnostic information has already been obtained by ACTA-scanning in such

diseases of the spinal cord as syringomyelia and certain tumors. In the area of spinal cord injury, it is anticipated that such techniques will be helpful in the assessment of certain aspects of cord injury, associated bleedings, and delayed cavity formation.

Nerve Growth and Regeneration

Scientists generally agree that restoration of useful function in the damaged central nervous system is a challenge without parallel. It is not one problem, but many, involving multi-faceted basic questions as to how a nerve cell and its fibers grow, how they know in which direction to grow, and how they make connections.

With the advent of new knowledge and techniques, scientists no longer consider the problem of regeneration insoluble. It is now known that two kinds of regeneration occur following injury to the central nervous system. One is terminal regeneration, in which an injured nerve simply regrows its severed process. The other is collateral regeneration, in which intact nerve fibers sprout additional outgrowths which reinnervate the adjacent denervated cells and thereby may establish function in place of the lost neurons.

To take advantage of these encouraging advances, the NINDS has established a Section on Neuronal Development and Regeneration within its intramural laboratories. Also, an ad hoc subcommittee of the National Advisory Neurological Diseases and Stroke Council recently completed a series of workshops on basic problems of regeneration. Summaries of the workshops reports together with the subcommittee's recommendations for future research will soon be presented to the Council. Publication of resulting position papers is also planned.

Rewards of Basic Research

Because of the meticulous step-by-step nature of basic research, its results sometimes take years, even decades, to evolve. Lives and entire professional careers are often invested in pursuing one small segment of a problem.

Even in the extraordinarily difficult research area of regeneration, however, identifiable progress is slowly being made. For example, Institute grantees, Dr. Rita Levi-Montalcini, Washington University, St. Louis, Missouri, and Dr. Stanley Cohen, Vanderbilt University, received the National Paraplegia Foundation's 1974 William Thomas Wakeman Award for basic research toward a cure for paraplegia. Their collaborative as well as independent findings over a 20-year period led to the discovery of a factor which is capable of enhancing the growth and development of nerve cells and their connections. While not a cure, this factor represents a valuable research tool.

Original work by another NINDS grantee, Dr. William F. Windle, Denison University, Granville, Ohio, while he was an NIH employee also exemplifies the evolutionary nature of basic research. It has recently become known that Dr. Windle's early demonstration of regeneration of nerve fibers across an experimental spinal cord lesion has stimulated efforts by Soviet scientists working in this field and, reportedly, has led to the development of a combined enzymotherapy and pyrogenal therapy for human subjects with acute spinal cord trauma. According to a preliminary report, these experimental treatments must be initiated immediately after an injury has been sustained. Through the US/USSR Health Exchange Program, Office of International Health, Department of Health, Education, and Welfare, the NINDS has proposed a conference with the Soviet scientists at which their findings could be discussed with U.S. scientists in the field of cord injury research.

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HEALTH SERVICES ADMINISTRATION

Maternal and Child Health

Children receiving health services in FY 72 from Title V assisted State Crippled Children's Programs included 95.5 with spina bifida and/or myelomeningocele. Of these, 19.7% or 1,876 were new cases referred that year. These children frequently require a range of services including hospitalization, treatment by a variety of medical specialists, and services from many health professions including nursing, social work, and physical and occupational therapy. Some children with spinal cord injuries also received services from the State Crippled Children's Programs. In general these efforts are directed towards helping the child achieve optimum function and are not those purely of maintenance.

Title V funds also support training and demonstration projects which provide model care for children with these conditions. Two projects, "The Project for Children with Handicapping Conditions," Dr. Mary Ames, the Children's Hospital of Philadelphia, and "Spina Bifida Demonstration and Service Clinic," Dr. Chester Swinyard, New York University Medical Center, have nationwide recognition for the care of these children and training of professionals to care for them. Many other Title V supported multidisciplinary clinics for handicapped children include children with spinal disorders in their caseload.

Some of the Title V research projects on the care of children with multiple handicaps have included children with myelodysplasia. One currently underway, "Cost and Utilization Patterns of Rehabilitation Service," Dr. David Macfarland, Crippled Children's Division, University of Oregon, includes an analysis of the total costs of care to the families of children with myelomeningocele. One project supported by the MCH special foreign currency program at the Institute of Mother and Child, Warsaw, entitled "Medical and Social Rehabilitation of Children with Myelomeningocele" demonstrated the need of a multidiscipline team for such cases.

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Such encouraging developments and the quarter century of careful investigation which preceded them could contribute to potential breakthroughs in paraplegic research. Most importantly such developments have signaled reexamination of the long-standing doubt that the central nervous system is capable of regeneration and have indicated the paths that future research must take.

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OFFICE OF HUMAN DEVELOPMENT

Rehabilitation Services Administration

It is estimated that there are more than 125,000 persons in the U.S. paralyzed as a result of spinal cord injury. In addition, approximately 8,000 to 10,000 new cases result each year. Most spinal cord injuries are the result of automobile, water, and contact sports accidents; industrial falls; and incidents of violence such as gunshot wounds.

Because of the catastrophic and astronomically expensive results of spinal cord injury, the Rehabilitation Services Administration has initiated a program of research to determine the rehabilitation benefits and cost effectiveness of a service delivery system dealing exclusively with spinal cord injury.

Ten Model SCI Systems have been initiated throughout the U.S. utilizing Rehabilitation Research and Demonstration Grant funds. The system concept includes emergency care and proper handling at the accident scene, sophisticated intensive care, a comprehensive program of rehabilitation services, vocational and educational preparation, and community placement with long-term follow-up services.

The total RSA spinal cord injury rehabilitation effort is developing into a coordinated and effective program through the utilization of both R&D and other Special Projects resources. The results of these projects are being developed into meaningful training programs and other effective methods by which State vocational rehabilitation agencies, private rehabilitation facilities or medical institutions can significantly improve and expand coordinative rehabilitation services to the spinal cord injured.

Due to the interests of other governmental agencies in the prevention, care, and treatment of SCI, the RSA has initiated collaborative activities with the VA, National Institutes of Health, and the Department of Defense in the interest of improved spinal cord injury rehabilitation.

The major emphasis of spinal cord injury research in the R&T Centers has been toward the prevention and treatment of costly complications, the development of new rehabilitation techniques, and the identification of psychological, social, and community characteristics that mitigate against successful rehabilitation and independent living. Approximately 40 projects are being conducted in these important areas.

In the research utilization and training areas, the R&T Centers have developed specific short-term clinical training programs for medical specialists and in-service training for rehabilitation counselors, social workers, physical and occupational therapists, and hospital administrators.

STROKE

Stroke (cerebrovascular disease) ranks third among causes of death in the United States, exceeded only by heart disease and cancer. Each year about 500,000 Americans are stricken, and about 200,000 die. Strokes incapacitate far more people than they kill, and are probably the leading cause of long-term disability in the United States. There are about 2.5 million stroke survivors in the country, 30 percent of whom have gone back to work or to their normal activity, with 55 percent disabled but capable of carrying on the activities of daily living, often with help. Fifteen percent are so helpless that total nursing care is required for the rest of their lives.

No detailed estimates of the monetary losses sustained by stroke victims can be made with available data, but a recent study commission proposed a figure of $1.2 billion per year excluding physician services and non-hospital care. Lives are stunted or for all practical purposes ended; families are disrupted or impoverished for months or years; and valuable contributors are lost to society. There are thus immense benefits to be achieved through research in this field--in both monetary and human terms.

The Department's activities in cerebrovascular disease are conducted by the National Institute of Neurological Diseases and Stroke (NINDS) with the cooperation of the National Heart and Lung Institute (NHLI) of the National Institutes of Health and by the Social and Rehabilitation Service (SRS). Stroke research is a major area of NINDS responsibility and has been given a very high priority in planning and development. Rehabilitation is the responsibility of SRS.

Obligations for Programs in Stroke (Cerebrovascular Disease)

	1972	1973	1974	1975 estimate	1976 estimate
National Institutes of Health:					
National Institute of Neurological Diseases and Stroke	$6,791,000	$6,983,000	$8,086,000	$8,578,000	$8,805,000
National Heart and Lung Institute	1,664,000	2,277,000	3,662,000	3,699,000	3,500,000
Subtotal, National Institutes of Health	8,455,000	9,260,000	11,748,000	12,277,000	12,305,000
Health Resources Administration:					
Regional Medical Programs Service	4,192,000	1,538,000	---	---	---
Total	12,647,000	10,798,000	11,748,000	12,277,000	12,305,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Diseases and Stroke

What is a Stroke? A stroke is a sudden loss of brain function resulting from interference with the blood supply to the brain. It is often the culmination of progressive cerebrovascular disease, which may extend over many years, and which is usually not detectable in the course of a normal physical examination. Some strokes are minor episodes, while others may cause death in a few minutes. Usually they are brought on by one of four events: thrombosis--a clot within a blood vessel of the brain or neck; cerebral embolism--the blocking of a blood vessel in the brain by a piece of clot or other material carried through the circulation from some other part of the body; narrowing (stenosis) of an artery supplying blood to the brain; or cerebral hemorrhage--the rupture of a cerebral blood vessel with bleeding into the brain tissue.

An important underlying cause of cerebrovascular disease is atherosclerosis. In atherosclerosis, fatty deposits form within the inner lining of an artery wall, and decrease the size of the channel carrying blood to the brain. Also, material from the deposits may break off and cause blocking of one of the cerebral arteries. High blood pressure (hypertension) also has been shown to be associated with a considerable increase in the frequency and severity of vascular diseases of the brain, especially cerebral hemorrhage. Among other causes of stroke are aneurysms and abnormalities in the clotting process. Aneurysms are sac-like swellings which may rupture, and are usually caused by congenital weaknesses in the artery walls. Abnormalities in the blood clotting mechanism may result in spontaneous hemorrhage.

Whatever the specific process involved, interference with the blood supply to the brain for more than about five minutes invariably leads to death of some brain cells and impairment of function. Temporary or permanent paralysis of movement, thought, memory, speech or sensation is the result.

Although the event of a stroke can be described in simple mechanical terms, cerebrovascular disease as a whole poses an extremely difficult set of medical, scientific and technical problems. The brain is an incredibly complex structure, with billions of delicate nerve cells and myriad interconnections and pathways. The circulatory system providing for its nutrition is correspondingly unique, complex, and delicate. Also, the brain and its supporting systems are placed within the relatively inaccessible bony skull. Scientists trained in many branches of biology and physics, as well as physicians skilled in clinical practice, must work closely together if cerebrovascular disease is to be well enough understood for man to intervene and prevent or cure it.

The NINDS Program

In the past 10 years, there has been a substantial increase in medical and scientific interest in cerebrovascular disease. This has been brought about in large part by the growth of the NINDS stroke program: in Fiscal Year 1974, Institute support for research in stroke reached a level of approximately $9.1 million, representing 30 research project grants, 15 clinical research centers, 11 acute care research units, 9 research contracts, and 21 intramural research projects. Additional support was provided for training in neurology and related disciplines and for relevant research in fundamental neurosciences, as well as for meetings and publications.

A small research program is conducted at the Institute in Bethesda, Maryland. At present this includes a study of non-acute cerebrovascular disease in young patients (up to 40), and animal studies aimed at possible salvage and preservation of brain tissue after a stroke. Also, the Institute has recently established a

Section on Head Injury and Stroke which is conducting, through contracts, a multi-institutional study of the hospital frequency and characteristics of transient ischemic attacks (little strokes). This study, which is in progress at six centers, will extend over three years, and will provide data on approximately 1,000 patients.

Clinical Research Centers

Cerebrovascular clinical research centers, located in large university medical centers across the country, now make up the largest segment of the program. These units, all of which are multidisciplinary, typically are staffed by as many as 15 to 20 scientists and physicians, plus technicians and other assistants. They vary in approach, some concentrating on single research areas, as at The Johns Hopkins University, where the epidemiological aspects of stroke are being studied. These include studies of incidence and prevalence, methods for early detection of "high risk" segments of the population, familial aggregation of stroke cases, and similar questions. A center at Boston University devotes its efforts entirely to research in aphasia, a speech disorder which often follows a stroke.

Other centers are broader in focus, often working with several approaches, such as the physical dynamics of blood flow, brain cell metabolism, pharmacology, surgery, the development of better methods of diagnosis and treatment, and many others. Generally, each center has an interrelated clinical and basic research program, and has accommodations for up to 30 research patients. All of the centers also conduct training programs for young physicians, scientists, and other workers.

Project Grants

In addition to the team efforts of the clinical research centers, smaller individual research projects are being conducted with Institute support. These range from basic laboratory studies in such fields as neurophysiology and biochemistry to clinical investigations of drug effectiveness, improvement of diagnostic devices and techniques, and development of improved surgical and medical treatment approaches. These smaller projects often produce information which is later exploited by the larger teams in the stroke research centers.

Collaborative Studies

One type of study which NINDS is uniquely able to sponsor, by reason of its resources and central role, is the cooperative study--the large-scale gathering and analysis of data from groups of institutions, using uniform definitions and methods. In this way, valid statistics can be produced and used as the basis for choices in research planning, and for improvements in treatment.

NINDS has sponsored several large cooperative studies in cerebrovascular disease. The largest, which has been in progress since 1958, has produced a large amount of data on the treatment of intracranial aneurysms, and subarachnoid hemorrhage. This year, the cooperating center for the study at the University of Iowa has reported notable success with an antifibrinolytic (clotting) agent known as epsilon aminocaproic acid, or EACA. Although not all investigators have agreed on its effectiveness, most users have found it to be the best immediate treatment for acute subarachnoid hemorrhage, and studies are now underway to find its exact mechanism of action.

One of the most damaging aftereffects of a brain hemorrhage is the increase of water (edema) in the tissues, and the congestion resulting from it. EACA seems to have a diuretic (edema relieving) effect as well as a clotting effect, making it doubly useful for these patients. In a new phase of the cooperative aneurysm study, a protocol is being developed in which eleven universities will supply data through which three treatments can be compared: EACA without dietary

fluid restriction, EACA with fluid restriction, and glycerol (another edema drug) with fluid restriction. The results of this study could provide valuable new information on treatment of hemorrhage, as well as a better understanding of the basic mechanisms of brain damage following hemorrhage.

Other Groups Working in the Stroke Field

The National Heart and Lung Institute (NHLI) supports some research relating to stroke. A major portion of its effort is devoted to atherosclerosis and hypertension research, aimed at elucidating the fundamental mechanisms of these disorders. A meaningful figure covering all of this work that bears a possible relation to cerebrovascular disease is not available, but the more directly stroke-related projects are estimated to total about $2.4 million annually. Also, within the Department of Health, Education, and Welfare, the Social and Rehabilitation Service (SRS) provides help to stroke victims. SRS provides grants for the training of rehabilitation workers, and approximately 7,200 stroke patients per year receive rehabilitation services through SRS-funded State programs. The Veterans Administration, through its 168 hospitals, provides medical services to many of the 28 million veterans in the U.S., and recorded 15,415 stroke patients in its hospitals in Fiscal Year 1974.

Outside the Federal Government, two national voluntary associations, the American Heart Association and the National Easter Seal Society for Crippled Children and Adults, have substantial interests in cerebrovascular disease. Fifty-two local chapters or State affiliates of the American Heart Association were supporting stroke projects in 1973, and the national office provided approximately $75,000 for research grants. The Easter Seal Society affiliates provided services to an estimated 16,000 stroke patients in Fiscal Year 1974. The National Health Education Committee, although it has no funds for services or research, operates a public information program in this field.

Large hospitals, medical schools, health departments, and hundreds of other institutions throughout the country provide stroke services or operate local programs benefitting stroke patients, but the entire national effort, individual and collective, is believed inadequate in view of the size of the problem.

Diagnosis

The diagnosis of cerebrovascular disease, on which treatment and, ultimately, prevention and preventive screening obviously depend, is still an inexact science. Accordingly, a large part of the total effort is directed toward finding better methods, and refinement and improvement of existing ones. The best of the presently established methods, X-ray angiography, comprises injection of radio-opaque dye into the neck arteries and subsequent X-ray examination of the head. The procedure, however, carries some risk of reaction to the dye, and the films are difficult to interpret because of the complexity of the circulation and the problem of obtaining depth or three-dimensional perception. Solution of the latter problem has been attempted through the technique of X-ray tomography, in which the picture is focused on a specific section or plane within the head. There is still the problem of shadows from tissues above and beneath the target area superimposed, out of focus, on the film.

Many other methods have been tried, including injections of radioisotopes and subsequent scanning with a radiation counting camera, ultrasound projection and translation of the echoes into a picture, recording of bruits, or abnormal sounds in the neck arteries, examination of retinal arteries, minute measurements of heat patterns radiating from the face or scalp, and various others. Except for the isotope scan, however, all of these methods are too limited to be extensively useful in clinical practice.

A new diagnostic technique, computerized soft tissue tomography, has been hailed by an NINDS grantee as "probably the most important advance in radiology

in 50 years." The technique, first developed commercially by an English company, EMI, Ltd., employs a narrow beam of X rays to rapidly scan the patient's head in a series of thin "slices." The beams pass through the head and hit two crystal detectors which feed signals into a high speed computer. At each of 28,000 points along the scan, the computer calculates the difference between the X rays originally emitted and those received on the crystals--the absorption coefficient--of the intervening tissues, blood, and bone. The computer also produces an oscilloscope picture for immediate viewing or photographic recording. The equipment is sensitive enough to detect differences in absorption of only one digit on a scale from -500 (air) to +400 (bone), and so far has been used to find cysts, tumors, abscesses, cerebral infarcts, intracerebral hemorrhages, and occasionally the plaques of multiple sclerosis. An important feature is that the instrument offers no danger or discomfort to the patient. More than 30 EMI scanners are now in operation in the United States. Most of the institutions housing cerebrovascular research centers have the equipment. A scanner has been ordered by the National Institutes of Health, with joint funding by NINDS, the National Cancer Institute, and the Clinical Center.

Ultrasound appears to have considerable promise in medical diagnosis generally, and in some aspects of cerebrovascular diagnosis. Analogous to sonar, it has been used for some years to locate the midline of the brain, which may be displaced to one side by edema (abnormal accumulation of fluid) or hemorrhage following a stroke. Scientists in one of the Institute-supported stroke research centers at Bowman Gray School of Medicine have been using ultrasound for determining blood flow through the carotid (neck) arteries. The carotid arteries are of special interest to stroke researchers, because they are a common locus of clots or atherosclerotic plaques which may cause blockage leading to a stroke. If the clots or plaques can be detected before they completely block the arteries they can be surgically removed and strokes prevented.

The Bowman Gray scientists' study showed that ultrasound can be used to screen patients for this one hazard--carotid occlusions, and that while some false positive results may occur, no patients with occlusions would be missed. Ultrasound equipment is relatively inexpensive, and has a number of other advantages. Studies like this one are of special importance because there are presently no other techniques for clinical evaluation of cerebral blood flow that are non-invasive.

Treatment

Progress in treatment of cerebrovascular disease is based on many small but significant improvements rather than any striking advances. Treatment varies according to the stage of the illness and the type of problem encountered. No one new procedure or development is expected to affect the prospects for all patients, but mention of a few provides a measure of progress and the generally optimistic outlook.

Surgery

In the past, cerebrovascular surgery has been limited almost entirely to correction of flaws or blockages (aneurysms, malformations, etc.) in the larger arteries such as the carotid arteries in the neck, which are relatively accessible. In recent years, intracranial arteries have come within reach of the surgeon. With the operating microscope, it is possible to remove clots from very small vessels, and also to make grafts of very small blood vessels (down to one millimeter in diameter) in order to bypass aneurysms and provide collateral circulation.

Of special interest have been recent attempts to channel blood into the brain from the scalp arteries, through holes drilled in the skull. Nearly 400 patients, mostly in Europe, but some in the United States, have undergone this procedure. The Institute's Section on Head Injury and Stroke, in collaboration with the National Naval Medical Center, have reported from animal studies the

effects of these grafts on regional cerebral blood flow and on its autoregulation, and have measured significant increases in blood flow and persistence of autoregulatory mechanisms despite some instability. However, this technique is still experimental and will require careful evaluation before it is introduced into routine medical practice.

A novel approach to the surgical treatment of cerebral aneurysms and other vascular defects was reported this year by grantees at Massachusetts General Hospital. These investigators have been experimenting with powerful magnets, which are used to guide catheters into small branches of the cerebral arteries that are otherwise inaccessible. So far limited to animals, the work has demonstrated that artificially produced aneurysms can be thrombosed--or plugged--with detachable silver plated catheter tips, and that the tips can be held in place magnetically until clotting seals off the aneurysm. This group also is working with ferrofluid--a carrier liquid containing extremely small particles of an iron compound. The ferrofluid can be fed into aneurysms via a catheter, and then held there by an external electromagnet until the aneurysm is filled and sealed off by fibrin and clotted blood. The procedure, if successful in humans, could replace major brain surgery for many patients with arteriovenous malformations and carotid cavernous fistulae as well as aneurysms, and could very favorably affect patient survival as well as health care costs.

Drugs

A broad-scale search continues for better drugs for treating cerebrovascular disease. Anticoagulants are commonly used in non-hemorrhagic strokes, as are blood pressure lowering agents. Efforts are being made to evaluate clot dissolving (thrombolytic) agents, and drugs that relax the brain blood vessels and allow them to open to their fullest diameter (vasodilators). Several drugs now are given to control the edema following strokes, and anesthetics have been used successfully to control the arterial spasms following subarachnoid hemorrhage.

Drugs that reduce the tendency of blood cells to stick to one another, including one of the most familiar drugs in existence--aspirin--are being increasingly studied. The chemical mechanism whereby aspirin inhibits platelet aggregation remains to be elucidated, but grantees at the Mayo Clinic in Rochester, Minnesota are exploring a number of hypotheses. One is that aspirin acts by combining chemically with the platelet membrane; another is that it combines with one or more plasma proteins, which in turn affect platelet function. A third hypothesis is that aspirin inhibits an enzyme in the membrane, and it also is considered possible that it inhibits synthesis in the platelets of several hormones. The Mayo scientists now are separating various blood and blood cell components in order to identify the fraction or fractions that take part in aspirin's action. The work could have great importance in leading to better understanding of the mechanism of clotting, which occurs in the majority of strokes.

Another possible research approach to drug treatment in stroke has come from the National Institutes of Health. An NINDS scientist who has done extensive work in enzyme replacement therapy in several rare neurological disorders, has found that it is possible, by injection of an enzyme, to quickly reduce to normal the amount of one type of fat (ceramide trihexoside) circulating in the blood of patients with Fabry's disease. (Fabry patients have a genetic deficiency of the enzyme which normally disposes of this fat, and blood levels are elevated to three times the normal. Many patients with this metabolic disorder suffer from a profound narrowing of the cerebral and myocardial blood vessels, and many have severe strokes; in fact, this is a principal cause of death in Fabry patients.)

The NINDS group now is planning studies aimed at learning whether this reduction of blood fat levels can reverse the arteriosclerotic process in these patients. If so, these studies could provide exciting new leads to the mechanisms

of arteriosclerosis in other patients, as well as a possible treatment for atherosclerotic cerebrovascular disease.

Stroke Acute Care Research Units (SACRU)

Since 70 to 80 percent of stroke mortality occurs within the first 10 days, and since the outlook for survival depends heavily on the quality of care during this critical period, the need for better "acute care" is obvious and urgent. In an effort to focus medical attention on this problem, the Institute has begun a program of acute care research units in 11 university medical centers and hospitals. These units are being equipped for precise monitoring of vital signs and levels of brain function, and are oriented toward the prevention of small strokes as well as the treatment of the acute phases of major strokes. The units resemble the intensive care units that have been so successful in managing coronary disease, except that they are concerned with research on the brain, as well as providing a needed training resource for physicians, interns, and other hospital personnel.

Epidemiology

Statistical studies of cerebrovascular disease in large groups of people hold promise both of identifying causes and of large-scale prevention. The Institute is supporting several epidemiological studies in stroke, in addition to The Johns Hopkins Center devoted entirely to this field.

For many years, distinct differences in morbidity and mortality from stroke in different parts of the United States have appeared in statistical tables. Whether these differences are real, or merely reflect differences in reporting, has been a major question.

Since high blood pressure is a leading precursor of stroke, the Institute is sponsoring, through The Johns Hopkins Center, a large study of blood pressure in the populations of three cities showing a wide variation in stroke mortality: Pueblo, Colorado, where it is low; Hagerstown, Maryland, where it is intermediate; and Savannah, Georgia, where it is high. Studies of possible contributory factors include: serum cholesterol, plasma glucose, obesity, cigarette smoking, and salt intake. The one striking element is a higher incidence of hypertension among blacks and efforts are concentrated on finding out why this is so.

A study begun last year in Panama may throw some light on the question. An unusual opportunity exists in Panama to study several geographically distinct Negro populations living in different environmental situations without encountering the high mobility and rapid urbanization factors which complicate studies in the United States.

The Panamanian populations include two groups of descendants of West Indian Negroes brought to Panama as laborers on the Canal between 1880 and 1913, one living a typical urban life in the Canal Zone, and the other in the relatively isolated Bocas del Toro district in a subsistence economy. Urban Canal Zone and remote dwelling descendants of Spanish slave laborers also are being studied, providing a mix of two genetic and two economic subgroups. The approach is to study incidence of hypertension as a risk factor in a black population with fairly common heredity but with differing environmental backgrounds extending back several generations. Valuable data from this study is expected within the next several years.

Outlook

There continue to be many urgent needs in the field of cerebrovascular disease. With increasing numbers of Americans moving into age groups at risk for stroke, continued research is important, both for stroke prevention and improvement in the quality of life for stroke victims. Recent evidence developed

by the World Health Organization (WHO) in the Indian subcontinent and Southeast Asia indicates that stroke is emerging as a leading problem among young adults in that part of the world. Discussions are underway between the NINDS and clinical scientists in India regarding a possible collaborative stroke study in that country.

OFFICE OF THE DIRECTOR

WITNESSES

LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
DR. RONALD W. LAMONT-HAVERS, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. Now we will hear from the NIH, Office of the Director. This presentation will be made by Mr. Leon Schwartz, Associate Director for Administration, National Institutes of Health.

We have your statement and biographical sketch which, I think, we can place in the record.

[The biographical sketch follows:]

Name: Leon M. Schwartz.
Position: Associate Director for Administration, NIH.
Birthplace and date: Baltimore, Md., April 26, 1928.
Education: A.B., economics, Johns Hopkins University, 1950.
Experience: Associate Director for Administration, NIH, January 1972–present. Deputy Assistant Director for Program Management, Research Applications Directorate, National Science Foundation, 1971. Assistant Commissioner for Administration, Office of Education, DHEW, 1968–1971. Deputy Assistant Commissioner for Administration, Office of Education, DHEW, 1967–1968. Goddard Space Flight Center, National Aeronautics and Space Administration, 1960–1967. Chief of Program Review and Resources Management, 1966–1967. Director of Program Support Division, 1965–1966. Business Manager, Meteorology Satellite Program, 1962–1965. Financial Cost Analyst, 1960–1962. Assistant Treasurer and Chief Accountant, Carpel Inc., 1954–1960. Part-time instructor, accounting, Baltimore Institute, 1958–1963.
Association memberships: Maryland Association of Certified Public Accountants. Federal Government Accountants Association. American Society for Public Administration.
Special awards, citations or publications: Certified Public Accountant. HEW Superior Service Award, 1970. Consultant to National Science Foundation, Advisory Panel for the Research Management Improvement Program, 1973–1974.

[The general statement follows:]

STATEMENT OF THE ASSOCIATE DIRECTOR FOR ADMINISTRATION

Mr. SCHWARTZ. Mr. Chairman and members of the committee, the appropriation for the Office of the Director provides for the central executive direction and management of the various programs of the National Institutes of Health. Specifically, this appropriation includes the Director and his immediate staff and the offices responsible for program planning and evaluation and public and scientific communications, and supporting management functions, involving budget and financial management, personnel management, contracts and grants management, and management analyses and reviews.

The functions and responsibilities of this appropriation are carried out through the offices of various associate directors and their supporting staff.

RESEARCH MANAGEMENT AND PROGRAM SERVICES

The Director's immediate office includes his principal associates who assist him in policy development and coordination of the extensive extramural, intramural, and collaborative programs of the Institutes and Research Divisions, and the programs of the National Library of Medicine. Staff offices responsible for program planning and evaluation and for public and scientific communications support the Director in carrying out these responsibilities.

The central management and program services financed by this appropriation support not only the overall management of the National Institutes of Health, but also provide a number of services to the individual Institutes and other operating components. Since most of the National Institutes of Health is located within a single geographical area, it is, therefore, expeditious and economical to provide a large number of management and program services on a consolidated central basis. These services financed through this appropriation include: budget formulation and execution, financial reporting and analysis; central accounting, voucher auditing and payment services for all of our appropriations and budget accounts; position classification and salary administration, equal employment opportunities, and a wide range of other personnel management services for over 11,000 employees; contracts and grants management services relating to more than 23,000 projects; and management studies and reviews which promote economies and efficiency of operations and insure effective application of policy and procedural controls throughout all of the operating components of the National Institutes of Health. The Office of the Director is taking the lead in conducting manpower utilization studies to insure that, where measurable, productivity continues to increase as the complexity and size of the NIH program grows.

FACILITY RENTALS

Included in this appropriation are funds to reimburse the GSA for NIH facility rentals in accordance with Public Law 92–313. This law provides that each agency occupying space assigned by GSA to reimburse the GSA for the space at a rate established by the Administrator and approved by OMB.

APPROPRIATION REQUEST

Mr. Chairman, the appropriation request for the Office of the Director is $19,986,000 for 1976, an increase of $2 million over the 1975 comparable level of $17,986,000. This requested increase of $2 million does not provide for any program increase and is entirely attributable to mandatory costs—that is, increased payments to GSA for facility rentals, increased payments to the NIH management fund, within-grade increases, annualization of the 1975 pay increases, and the like.

Thank you. I shall be happy to respond to any questions you may have.

FACILITY RENTALS

Mr. FLOOD. In your statement you say that part of that $2 million increase that you are asking for in the budget, is attributed to increased payments to GSA for what you call facilities rentals. How much of the total increase is for that item?

Mr. SCHWARTZ. $1,010,000 is for the facilities increase.

Mr. FLOOD. Does this increase in rental cost stem from the fact that you are renting more space in 1976 than you were in 1975?

Mr. SCHWARTZ. No, sir.

The amount of space we are renting is exactly the same. It comes from three different categories of increase assessed by GSA.

Mr. FLOOD. If the amount is the same, then how did you compute that increase?

Mr. SCHWARTZ. Part of the increase is based on a unit rate change that is assessed by the GSA. They review all of our rental facilities, go through an evaluation, and then based upon the evaluation they then come out with a quality of space assessment.

They then apply the appropriation rate. It is partially that.

Mr. FLOOD. They do that?

Mr. SCHWARTZ. Yes, sir, that is something GSA does. We have also had some increase in our recurring costs. We have had additional security coverage and some of the utility costs have gone up.

This part of the increase amounts to about $243,000.

The first category, by the way, I mentioned of rate and category change amounted to an increase of about $400,000. They have also assessed us with a restoration.

Mr. FLOOD. They?

Mr. SCHWARTZ. GSA, with a restoration of the 10-percent reduction made by the subcommittee last year.

Mr. FLOOD. In this rental space, is most of that for the general purpose office space or is it mostly for the research space?

Mr. SCHWARTZ. It is primarily general office space. We do have some warehouse space and we have some small facilities associated with research.

Mr. FLOOD. On your research rental space, do you pay a standard level charge there?

Mr. SCHWARTZ. There is very little that is of a research nature. However, on this space we do pay a specific charge, yes, sir.

Mr. FLOOD. On that table you have on 1281, will you update that from last year's hearings?

Mr. SCHWARTZ. Yes; we will be glad to.

[The information follows:]

STANDARD LEVEL USERS CHARGES—FISCAL YEAR 1976, RENTAL SPACE

	Office space square feet	Staffing	Other space square feet	Staffing	Total Square feet	Total Staffing	Annual rental fee—fiscal year 1976
Auburn Bldg			[1] 19,405	62	19,405	62	275,043
Blair Bldg	53,136	194	[2] 864	3	[3] 54,000	197	394,990
Federal Bldg	87,090	363	[4] 18,232	1	105,322	364	748,137
Landow Bldg	95,183	501	[5] 4,429	4	99,612	505	786,167
Westwood Bldg	157,415	763	[6] 221,390	16	378,805	779	1,507,441
Westwood Annex Bldg	56,055	351			56,055	351	357,502
Danac Warehouse			60,000	15	60,000	15	101,400
NIEHS Warehouse	500	4	17,135	6	17,635	10	21,261
Akin and Flanders Bldg	6,128	26	[7] 25,552	15	31,680	41	123,885
Perrine, Fla			977	4	977	4	4,196
Total	455,507	2,202	367,984	126	823,491	2,328	[8] 4,320,022

[1] Contains 19,405 square feet of laboratory and laboratory support space.
[2] Includes 581 square feet of automatic data processing space.
[3] Estimated.
[4] Includes 15,000 square feet of parking space and 635 square feet of clinical support space.
[5] Includes 747 square feet of automatic data processing space.
[6] Includes 2,929 square feet of automatic data processing and printing space and 210,000 square feet of parking space.
[7] Includes 13,800 square feet of parking space and 5,947 square feet of special purpose space.
[8] Includes $408,628 for direct security and utilities costs.

Mr. FLOOD. Bring that up to date. Be sure to break out that special purpose space.

Make that special purpose space jump out.

Mr. SCHWARTZ. Yes, sir.

PATIENT CHARGES AT CLINICAL CENTER

Mr. FLOOD. Last year you said that NIH submitted a staff paper over to the Secretary on the subject of patient charges in the clinical center. What is the current status of that issue? What happened to that?

Mr. SCHWARTZ. The Secretary has decided that the current policy of not charging for the clinical center patients and not attempting to get third party reimbursement should stand. There has been no change in the NIH policy.

STAFFING

Mr. FLOOD. Now, most of the Institutes in NIH show reductions in the staffing in fiscal year 1976. Is that reduction of personnel they were all talking about a result of NIH contracting for services that would normally be done by the regular Federal employees or what?

Mr. SCHWARTZ. No, sir. NIH had to take our share of the overall reduction in Federal employment and we have taken this by some readjusting of current activities, not by contracting out.

Mr. FLOOD. Something new happens here every day. Here is one: We are experiencing a pretty new phenomenon. We are getting all kinds of letters now, mostly from university medical researchers. They are urging us to do something about lifting the ceiling on Federal salaries. We are getting stacks of these letters. They are concerned, they say, that if the current ceiling remains as it has for a very long period of time, that you are going to lose a lot of outstanding scientists working with the intramural research programs.

Are you encountering difficulties now in retaining and recruiting the scientists for your intramural programs?

Mr. SCHWARTZ. Yes, we certainly are.

I thing Dr. Lamont-Havers has been heading up several search committees and would like to elaborate.

Mr. FLOOD. You have a good lobby going for you. Somebody is doing a proper job.

Dr. LAMONT-HAVERS. I think the biomedical community is concerned now.

We are right now trying to recruit for four Institute Directors, for heart and lung, for aging, for allergy, and for dental research. We just cannot get the leadership that the biomedical community themselves require for these areas.

Mr. FLOOD. I remember you mentioned that, that is right. Is it all the way down the line?

Dr. LAMONT-HAVERS. Yes, sir.

Mr. FLOOD. I can understand having trouble with the top brass.

Dr. LAMONT-HAVERS. We are trying to recruit an obstetrician who knows something about research to head a laboratory in the Child Health Institute. It is virtually impossible.

Mr. FLOOD. Can you give us a comparison of a salary paid to a principal investigator under the extramural research grant with the salaries paid to a NIH scientist with comparable credentials and comparable appearance?

Dr. LAMONT-HAVERS. Yes, sir.

Mr. FLOOD. Give us about half a dozen examples.

Mr. SCHWARTZ. We also have statistics on salary structure in universities. I think that has a relationship.

Mr. FLOOD. Give us a half dozen examples.

This record will have to look pretty good on that, too.

[The information follows:]

COMPARISON OF SALARIES PAID TO PRINCIPAL INVESTIGATORS AT NIH WITH THAT OF PRINCIPAL INVESTIGATORS AT UNIVERSITIES RECEIVING NIH GRANTS

Senior principal investigators at NIH (that is, Laboratory and Branch Chiefs) in the civil service are primarily in supergrade positions and receive $34,000 to $36,000 annually. A survey of seven universities and research institutions receiving NIH grants has revealed that their principal investigators receive from $38,000 to $90,000 total salary (which may in part come from grant funds) with an average salary of approximately $54,000.

COMPARISON OF SALARIES OF NIH SCIENTISTS WITH UNIVERSITY FACULTY

The crisis in attracting and retaining the staff necessary to the continuation of the NIH mission exhibits itself most clearly and dramatically at the very top levels of the Agency. Until about 1970, the NIH was able to attract the highest quality staff to provide program direction and guide its laboratory and clinical programs. This is no longer true. The NIH positions of Institute Directors, as well as associate clinical and scientific directors, are generally recruited from deans and department chairmen in medical schools. Similarly, laboratory and branch chiefs are recruited from senior professional positions. Because of the $36,000 salary limitation, NIH can no longer compete successfully for outstanding scientific leaders.

The 1973–74 AAMC medical school faculty salary study reveals the nature of the problem. Department chairmen in medicine are paid base salaries that average $49,700; professors are paid an average of $39,000; chairmen of anesthesiology, pathology, and radiology departments receive $49,000–$55,000, while professors average $40,000–$43,000. In addition, most physicians receive supplemental income from outside medical practice and consultation. University systems also provide generally superior fringe benefits, such as free retirement and health insurance, and tuition waivers for children. The NIH is now caught in a vicious circle of not being able to recruit and retain top level staff which further deteriorates our

research abilities and progressively makes NIH less attractive as a place to do high quality research.

This phenomenon centers so strongly around individuals and levels of positions that it is not amenable to statistical representation. However, the facts are that Institute Director positions remain unfilled for a year or longer. The Insitutes are no longer able to attract the highest quality staff to lead laboratory and clinical programs and the Clinical Center is in a continuing crisis situation because of the inability to recruit anesthetists, radiologists, and other professionals necessary to quality patient care.

Since the passage of the variable incentive pay bill implemented in September 1974, 22 civil service medical officers employed by NIH have converted to commissioned corps status. Mostly these have been senior staff members whose remuneration thereby has increased by several thousand dollars annually, frequently exceeding the statutory $36,000 limit for civil service employees. Even so, the most a "principal investigator" could receive in the Corps is $46,800 and that would be with 26 years service.

Mr. FLOOD. Last year Dr. Stone mentioned that the salaries paid to the uniform staffs of university medical schools would be higher than the salaries elsewhere in the whole government. Now in view of the fact that that facility will be built across the street from NIH, are you running into any morale problems based upon this salary differential you were talking about?

Dr. LAMONT-HAVERS. We are running into problems because there it is across the road. Obviously recruitment is shifting. There obviously will be morale problems which will be intensified once that new medical school gets going. Right now there are not that many people appointed, so that they cannot quite see what they are dealing with, but it will become a very severe problem.

MANPOWER UTILIZATION

Mr. FLOOD. Last year you told us you conducted what you called a pilot program in manpower utilization. That involved the extramural program at the Allergy Institute. Have you expanded that effort into any of the other Institutes?

Mr. SCHWARTZ. Yes, sir.

We now have the Cancer Institute and the Dental Institute under the program with very useful results.

Mr. FLOOD. Has it been successful?

Mr. SCHWARTZ. Yes; the Cancer Institute developed their budget this year on the basis of that study.

They were able to start off with the expected dollar level, convert that into number of grants and contracts to be managed and then upon the basis of standard manpower utilization figures they were then able to determine the appropriate staff.

Mr. FLOOD. Then this is a good thing.

Mr. SCHWARTZ. Yes, sir, it certainly is.

Mr. FLOOD. Is this manpower utilization program an on-going program or is it something you did once in order to comply with a directive from OMB and that is the end of it?

Mr. SCHWARTZ. No, sir, it is on-going. We expect over a 3-year period to cover all of our institutes.

MANAGEMENT OVERVIEWS

Mr. FLOOD. Last year you told us that in fiscal 1975 you planned to schedule a number of management overviews on on-going grantees. Did you undertake these studies? What did you find out?

Mr. SCHWARTZ. Yes, sir.

We have actually conducted studies and reviewed many audit reports. Based upon these studies, we have come up with general problems that are generic in all universities. From this we intend to put out a series of bulletins to the universities pointing out some of the special problems.

One special problem we are already working on is the fact that equipment is being underutilized in many universities. We have been working with the National Science Foundation in developing what might be a pilot equipment program that would be available for the use of all universities.

Mr. FLOOD. Is this kind of what you call management overview going to help you contain this upward spiral of the amount of the indirect costs paid to these grantees?

Mr. SCHWARTZ. It might be helpful, Mr. Flood. I think that is a problem that will not be cured just by a management review like this. It is reflective of increasing costs.

Mr. FLOOD. I didn't say cure. But will it help?

Mr. SCHWARTZ. I think it might help, yes, sir.

Mr. FLOOD. Mr. Patten.

Mr. PATTEN. No questions.

Mr. FLOOD. Mr. Conte.

EQUAL EMPLOYMENT

Mr. CONTE. Would you describe your EEO program as it has operated during the past year?

Mr. SCHWARTZ. The overall Equal Employment Opportunity Program for the National Institutes of Health is administered through a central office reporting to the Director, National Institutes of Health. The central EEO office is managed by the Equal Employment Opportunity officer assisted by his staff which includes a deputy, program manager, Federal women's program coordinator, complaints manager, and a Spanish-speaking program coordinator. In addition, the National Institutes of Health has Equal Employment Opportunity counselors widely spread throughout the campus. The EEO counselors report directly to the Equal Employment Opportunity officer in their roles as counselors. Also, the major bureaus and institutes within the NIH have appointed Equal Employment Opportunity coordinators who are responsible for providing programmatic guidance and direction. We feel that our program has been effective, including several new initiatives during the last year, such as establishment of a minority and women recruitment staff, conducting minority cultural programs, and carrying out a major meeting of predominantly minority and women's colleges for discussing extramural programs as well as possible NIH employment opportunities. Our backlog of formal EEO complaints has been reduced from 26 to 4 during this year.

Mr. CONTE. Have there been advances in the numbers of women and minority groups employed at NIH? Do you have data on the numbers of these who have been at professional and supervisory level positions?

Mr. SCHWARTZ. Yes; advances have been made in the numbers of women and minority groups employed at NIH. During the past year NIH increased its full-time employment by 77 minorities and 170 women. Our total full-time work force on January 1, 1975, contained 27 percent minorities and 46 percent women.

Most of the GS–9 and above positions are considered professional or supervisory positions. In the past year, the increase in full-time GS–9 and above employees were 72 for minorities and 138 for women. On January 1, 1975, of the general schedule employees at NIH at GS–9 or above, 14 percent were minorities and 39 percent were women.

MANPOWER UTILIZATION

Mr. CONTE. Would you tell me about your manpower utilization studies? How do you measure productivity in an area like biomedical research?

Mr. SCHWARTZ. Manpower studies have been utilized in our nonresearch positions covering such areas as grant and contract management, clinical services, and logistical support. As of fiscal year 1974 about 40 percent of these nonresearch positions were covered by such studies and we estimate 70 percent coverage by the end of fiscal year 1975. We anticipate that out of this effort we will develop an agency-wide workload/manpower monitoring system that will assist us in forecasting, allocating, and utilizing our manpower resources.

NIH does not attempt to measure productivity in the biomedical research programs by using manpower utilization studies. Productivity is assessed by a variety of evaluation criteria which include peer review of progress, quality of scientific publications, and other indications of achievement such as external awards or recognition.

MANAGEMENT FUND

Mr. CONTE. Why does your office make payments to the NIH management fund? It seems that you are the NIH management.

Mr. SCHWARTZ. The Office of the Director receives and is assessed for certain common supporting services which are required in operating the National Institute of Health. The services for which we are assessed include the maintenance of buildings and grounds, housekeeping and sanitary services, transportation which includes the operation of the NIH motor pool, security and fire protection, supply and procurement, etc. We make payments to the NIH management fund to support these common services just as every NIH operating appropriation does.

The Office of the Director is a distinct appropriation that is responsible for the overall direction and management of the NIH and is not an activity of the NIH management fund which provides for NIH-wide services.

POSITION DECREASES

Mr. CONTE. Why do you have a decrease of three positions for research management?

Mr. SCHWARTZ. The decrease of three positions amounted to our share of the overall reduction of NIH positions.

DISSEMINATION OF RESEARCH FINDINGS

Mr. CONTE. Can you tell me about your strategy for disseminating NIH research findings? How do your results get into the health care delivery system?

Mr. SCHWARTZ. The individual Institutes each have Offices of Scientific and Technical Reports which originate and supply a great many informational materials on research findings to scientists, practicing health professionals and the general public. A wide variety of media and methods are used.

At the presentation of Dr. Lamont-Havers opening statement, he provided the subcommittee with copies of a study on dissemination of research findings which was completed March 7, 1975, by a committee of senior NIH administrators, scientists and communication personnel on the entire range of activities related to research information dissemination. This report and its recommendations describe the basic NIH plans and strategy for transfer of research information. The report deals particularly with dissemination to practicing health professionals.

MANAGEMENT FUND DATA BOOK

Mr. CONTE. What is the Management Data Book?

Mr. SCHWARTZ. The Management Data Book is a monthly publication which provides management with a comprehensive overview of resources and the status and trends of major programs and operations at the NIH. Some of the items included in this publication are: manpower data, obligation and expenditure data, grant and contract data, and the status of operational planning objectives. This data book is designed to assist management in identifying and analyzing problems and making informed decisions.

UPWARD MOBILITY

Mr. CONTE. Would you tell me about the upward mobility program and how it is being redesigned to meet the needs of NIH?

Mr. SCHWARTZ. The NIH upward mobility program is comprised of 6 structured programs with the participation of approximately 430 employees. One of these structured programs known as Stride provides competitively nominated employees with training in selected on-job-training assignments coupled with appropriate collegiate education. Upon completion of this program, the graduates are placed in professional positions at NIH. Recognizing our commitment to place these Stride graduates, NIH developed manpower projections for its pattern of hiring baccalaureate professional. Based on these projections, training opportunities in the Stride program were allocated accordingly. A significant outcome of these manpower projections was the development of a new training component within Stride for the training of registered nurses to meet a critical NIH need at the Clinical Center.

We have also proposed an apprenticeship program to develop skilled craftsmen to meet the demands required for plant maintenance at NIH. This presently proposed program is waiting approval of the Civil Service Commission and the Department of Labor.

Mr. CONTE. Thank you.

Mr. FLOOD. Thank you, Mr. Schwartz.

Mr. SCHWARTZ. Thank you, sir.

Justification of the Budget Estimates

Appropriation Estimate

OFFICE OF THE DIRECTOR

For expenses necessary for the Office of the Director, National Institutes of Health, [$17,000,000] *$19,986,000*

Funds advanced to the National Institutes of Health management fund from appropriations in this Act shall be available for the expenses of sharing medical care facilities and resources pursuant to section 328 of the Public Health Service Act and for the purchase of not to exceed [fourteen] *thirteen* passenger motor vehicles for replacement only.

For "Office of the Director" for the period July 1, 1976, through September 30, 1976, $4,997,000.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Amounts Available for Obligation 1/

	1975 Estimate	1976 Estimate
Appropriation.....	$17,000,000	$19,986,000
Proposed supplemental	326,000	---
Subtotal, adjusted appropriation.	17,326,000	19,986,000
Comparative transfers from:		
"National Cancer Institute".....	55,000	---
"National Heart and Lung Institute"...	37,000	---
"National Institute of General Medical Sciences".....	30,000	---
"National Institute of Child Health and Human Development".....	25,000	---
"Fogarty International Center"..... (Transfer of funds for Public Affairs Reorganization)	45,000	---
"National Cancer Institute".....	78,000	---
"National Heart and Lung Institute"...	111,000	---
"National Institute of Dental Research"	9,000	---
"National Institute of Arthritis, Metabolism and Digestive Diseases"..	65,000	---
"National Institute of Neurological Diseases and Stroke".....	44,000	---
"National Institute of Allergy and Infectious Diseases".....	37,000	---
"National Institute of General Medical Sciences".....	58,000	---
"National Institute of Child Health and Human Development".....	36,000	---
"National Institute of Aging".....	4,000	---
"National Eye Institute".....	17,000	---
"National Institute of Environmental Health Sciences".....	6,000	---
"Fogarty International Center".....	1,000	---
"National Library of Medicine"..... (Transfer of the Institutional Relations Branch from the Division of Research Grants, NIH Management Fund)	2,000	---
Total obligations.....	17,986,000	19,986,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 - $9,100,000; 1976 - $9,100,000.

Summary of Changes

1975 Estimated obligations	$17,986,000
1976 Estimated obligations	19,986,000
Net change	+2,000,000

	1975 Base Pos.	1975 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
Built-in:				
1. Facility rentals	---	---	---	+$1,010,000
2. Payment to NIH Management Fund	---	---	---	+493,000
3. Annualization of pay increases	---	---	---	+191,000
4. Within-grade pay increases	---	---	---	+177,000
5. Annualization of health benefits	---	---	---	+35,000
6. Extra day of pay	---	---	---	+39,000
7. Bureau of Employment Compensation, Federal Telecommunications System, postage, and service and supply rate increases	---	---	---	+55,000
Total, increases	---	---	---	+2,000,000
Decreases:				
Program:				
1. Research management and program services	549	$17,986,000	-3	---
Total, net change	---	---	-3	+2,000,000

Explanation of Changes

Increases:

Built-in -- The increase of $2,000,000 will provide $1,010,000 for increased payments to GSA for facility rentals; $493,000 for increased payments to the NIH Management Fund; $191,000 for annualization of the pay increases; $177,000 for within-grade pay increases; $35,000 for annualization of health benefits; $39,000 for an extra day of pay in 1976; and $55,000 for Bureau of Employment Compensation, Federal Telecommunications System, postage, and service and supply rate increases.

Obligations by Activity

Page Ref.	1975 Estimate Pos.	1975 Estimate Amount	1976 Estimate Pos.	1976 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
Research management and program services	549	$17,986,000	546	$19,986,000	-3	+$2,000,000
Total obligations.....	549	17,986,000	546	19,986,000	-3	+2,000,000

Obligations by Object

	1975 Estimate	1976 Estimate	Increase or Decrease
Total number of permanent positions	549	546	-3
Full-time equivalent of all other positions	56	56	---
Average number of all employees	579	579	---
Personnel compensation:			
Permanent positions	$9,326,000	$9,665,000	+$339,000
Positions other than permanent	524,000	532,000	+8,000
Other personnel compensation	219,000	222,000	+3,000
Subtotal, personnel compensation	10,069,000	10,419,000	+350,000
Personnel benefits	940,000	1,017,000	+77,000
Travel and transportation of persons	129,000	129,000	---
Transportation of things	6,000	6,000	---
Rent, communications and utilities	3,748,000	4,772,000	+1,024,000
Printing and reproduction	323,000	323,000	---
Other services:			
Payment to NIH Management Fund	1,952,000	2,445,000	+493,000
Other	585,000	641,000	+56,000
Supplies and materials	132,000	132,000	---
Equipment	102,000	102,000	---
Total obligations by object	17,986,000	19,986,000	+2,000,000

Office of the Director

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1970	$7,930,000	$7,930,000	$7,930,000	$7,930,000
1971	10,886,000	10,886,000	10,886,000	10,886,000
1972	11,324,000	11,324,000	11,324,000	11,324,000
1973	12,423,000	12,423,000	13,423,000	12,423,000 1/
1974	12,993,000	12,993,000	12,993,000	12,993,000
1975	18,784,000	18,554,000	17,660,000	17,660,000
Proposed Supplemental	326,000			
1976	19,986,000			

1/ This appropriation was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate in the first vetoed bill.

Office of the Director

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1970	$7,093,000	$7,093,000	$7,093,000	$7,323,300
1971	8,206,000	8,206,000	8,206,000	8,903,000
1972	11,442,000	11,442,000	11,442,000	11,712,000
1973	12,042,000	12,042,000	13,042,000	12,042,000 1/
1974	12,000,000	12,000,000	12,000,000	12,000,000
1975	18,124,000	17,894,000	17,000,000	17,000,000
Proposed Supplemental	326,000			
1976	19,986,000			

1/ This appropriation was the continuing resolution. The appropriation amount was the House Allowance, which was the lower of the House or Senate in the first vetoed bill.

Justification

Research management and program services

	1975 Estimate		1976 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Personnel compensation and benefits	549	$11,009,000	546	$11,436,000	-3	+$427,000
Other expenses	---	6,977,000	---	8,550,000	---	+1,573,000
Total	549	17,986,000	546	19,986,000	-3	+2,000,000

General Statement

The Office of the Director appropriation provides for: (1) the overall direction of the National Institutes of Health, including the immediate office of the Director and the offices responsible for program planning and evaluation, and scientific and public communications; and (2) supporting management services including financial management, personnel management, management policy and review, and grant and contract management. The 1976 budget provides for no program increases. The only increases requested are mandatory increases which will permit the Office of the Director to operate at the 1975 comparable level.

Program Plans for 1975 and 1976

Executive direction of NIH will reflect a continuing emphasis on making the NIH organization an effective instrument for furthering and coordinating programs in support of biomedical research. This involves the collection and evaluation of data, the review and analysis of program issues and proposals, the appraisal of on-going programs, the development of policy position papers and the preparation of long-range program plans, as well as the preparation of information and its dissemination to the scientific and educational communities and to the general public.

The central management services financed by this appropriation support not only the overall direction and management of NIH but also provide a number of services to the individual Institutes and the other operating components of NIH. Financial management includes budget formulation and execution, financial reporting and analysis, grant payment and settlement, and accounting and voucher auditing for over 1,000 cost centers. Personnel management provides over 11,000 employees with a wide variety of personnel services, including training and employee development, classification and salary administration, employee and labor relations, equal employment opportunities, and recruitment and placement of a great variety of professional and support jobs. Management studies and reviews are undertaken to promote economy and efficiency of operations and to identify possible weaknesses in policy and procedural

controls. The central contracts and grants office provides policy leadership and guidance in the review and servicing of over 23,000 active on-going projects.

The requested mandatory increase of $2,000,000 consists of $1,010,000 for increased payments to GSA for facility rentals; $493,000 for increased payments to the NIH Management Fund; $191,000 for annualization of the 1975 pay increases; $177,000 for within-grade pay increases; $35,000 for annualization of health benefits; $39,000 for an extra day of pay, and $55,000 for Bureau of Employment Compensation, Federal Telecommunications System, postage and service and supply rate increases.

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Program Purpose and Accomplishments

Activity: Research management and program services

1975			1976 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
549	$17,986,000	N/A	546	$19,986,000

Purpose: The purpose of this activity is to provide overall program direction and central management services to the Bureaus, Institutes and Divisions of the National Institutes of Health.

Explanation: The functions and responsibilities of this activity are carried out through the offices of various associate directors and appropriate office directors with the aid of staff specialists and operating personnel.

Accomplishments in 1975: (1) Completed and made available for distribution the NIH Equal Employment Opportunity Manual. (2) Developed a quarterly review and reporting of progress by organizational units in the Affirmative Action Plan. (3) Made the reorganized Public Affairs Office fully functional and carried out many of the activities which were formerly the responsibility of the BID's. (4) Improved liaison with grantee institutions. (5) Prepared testimony and reports to Congress and prepared background material on major legislative issues. (6) Developed legislative proposals for the following pieces of legislation that will expire on June 30, 1975: National Heart, Blood Vessel, Lung, and Blood Act; National Sickle Cell Anemia Prevention and Control Act; and National Cooley's Anemia Prevention and Control Act. (7) Studied the feasibility of developing a methodology for allocating national expenditures for biomedical research by disease category and health problems. (8) Initiated systematic assessment of the impact of NIH, other Federal, and non-Federal support upon the research and research training capabilities of major academic and research institutions. (9) Developed more effective mechanisms for projecting future manpower supply/demand relationships. (10) Planned for a solid framework for comparing U.S. funds for biomedical research with outlays of major industrial and developing nations. (11) Developed and implemented a productivity and manpower measurement system. (12) Provided leadership in developing an improved strategy for dissemination of NIH research fundings. (13) Maintained and expanded the Management Data Book. (14) Established one centrally located office for all permanent changes of station, both civilian and Commissioned Corps, thus enabling all prospective travelers and administrative offices to obtain policy and current travel order status information in a more efficient manner. (15) Served as the Project Office for the design and implementation of the NIH Material Management System.

Objectives for 1976: (1) To provide for comprehensive planning, priority setting, resource allocation, and reporting and evaluation of program results. (2) To continue to respond to intensified Congressional interest in health, greater participation on task forces, development of regulations for the protection of human subjects in biomedical research, and increased court activity on freedom of information. (3) To effect an increase in the total number of minority and women professional placements in each BID and to increase their participation in policy and decision making areas throughout NIH. (4) DFM will serve as the Project Office for a Service and Supply Fund Uniform Cost Accounting System scheduled to be on-going in 1976. (5) An attempt will be made to computerize Central Budget Office formulation data to assist in the completion of OMB schedules and DHEW preliminary budget estimates. (6) Continued improvement in financial reporting by improving paper flow where possible and updating existing systems as new computer technologies are developed. (7) Expand the use of microfilm as a technique for internal data exchange and use for historical record keeping and to reduce the paper flow throughout DFM operations. (8) Coordinate systems programs with DHEW Regional Accounting Systems and Central Registry Systems for purposes of continued compatability. (9) Complete evaluation of the Upward Mobility Program and to redesign this program to meet the specific needs of NIH. (10) To complete development and implementation of a comprehensive Executive Development Program. (11) To promote excellence in the NIH research contracting and grants management program by continuing review and evaluation of BID contracting operations to develop the highest level of quality and by an intensified program of appraisal of institutional management of NIH grant funds.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Amounts Available for Obligation 1/

	1976 Estimate	Interim Period
Appropriation	$19,986,000	$4,997,000
Total, obligations	19,986,000	4,997,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $9,100,000; Interim Period - $2,275,000.

Obligations by Activity

	1976 Estimate		Interim Period	
	Pos.	Amount	Pos.	Amount
Research management and program services	546	$19,986,000	546	$4,997,000
Total obligations	546	19,986,000	546	4,997,000

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Obligations by Object

	1976 Estimate	Interim Period
Total number of permanent positions	546	546
Full-time equivalent of all other positions	56	14
Average number of all employees	579	145
Personnel compensation:		
Permanent positions	$9,665,000	$2,416,000
Positions other than permanent	532,000	133,000
Other personnel compensation	222,000	56,000
Subtotal, personnel compensation	10,419,000	2,605,000
Personnel benefits	1,017,000	254,000
Travel and transportation of persons	129,000	33,000
Transportation of things	6,000	2,000
Rent, communications and utilities	4,772,000	1,193,000
Printing and reproduction	323,000	81,000
Other services:		
Payment to NIH Management Fund	2,445,000	611,000
Other	641,000	159,000
Supplies and materials	132,000	33,000
Equipment	102,000	26,000
Total obligations by object	19,986,000	4,997,000

Justification

The estimate for the three-month interim period reflects a continuation of the programs of the Office of the Director consistent with the 1976 estimate. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1975 modified by program impact of the FY 1976 estimate.

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