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DEPARTMENTS OF LABOR AND HEALTH, EDUCATION, AND WELFARE APPROPRIATIONS FOR 1977

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HEARINGS

BEFORE A

SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS HOUSE OF REPRESENTATIVES

NINETY-FOURTH CONGRESS

SECOND 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 4

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 1977

TUESDAY, FEBRUARY 24, 1976.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

WITNESSES

DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. RONALD W. LAMONT-HAVERS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
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CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We now have the National Institutes of Health. The presentation will be made, of course, by Dr. Donald S. Fredrickson, who is the Director. We have a biographical sketch of you here, Doctor, which we will place in the record at this point.

[The material follows:]

CURRICULUM VITAE

Name: Donald S. Fredrickson.
Home address: 6615 Bradley Boulevard, Bethesda, Maryland.
Date and place of birth: August 8, 1924, Canon City, Colorado.
Family: Henriette Priscilla Dorothea Eekhof Fredrickson, two children.
Education: University of Colorado, 1942–1943; B.S., University of Michigan, 1946; M.D., University of Michigan, 1949. Certified: American Board of Internal Medicine, 1957.
Chronology of employment:
1949–1950, House Officer, Peter Bent Brigham Hospital, Boston.
1950–1951, James Jackson Cabot Research Fellow in Medicine, Harvard Medical School, Boston.

1950–1952, Assistant in Medicine, Peter Bent Brigham Hospital, Boston.
1952–1953, Research Fellow in Medicine, Massachusetts General Hospital, Boston.
1953–1955, Clinical Associate, National Heart Institute, National Institutes of Health, Bethesda.
1955–1961, Member, Senior Research Staff, Laboratory of Cellular Physiology and Metabolism, National Heart Institute.
1961–1966, Clinical Director, National Heart Institute.
1962–1966, Head, Section on Molecular Diseases, Laboratory of Metabolism, National Heart Institute.
1966–1974, Chief, Molecular Disease Branch, National Heart and Lung Institute.
1969–1974, Director of Intramural Research, National Heart and Lung Institute.
1974–1975, President, Institute of Medicine, National Academy of Sciences, Washington, D.C.
1975 to present, Director, National Institutes of Health.
Present academic appointments: Special Lecturer in Internal Medicine, George Washington University School of Medicine, Washington, D.C.; Lecturer in Preventive Medicine, Georgetown University School of Medicine, Washington, D.C.
Member: Alpha Omega Alpha; American Academy of Arts and Sciences; American Association for the Advancement of Science; American College of Cardiology, Fellow; American College of Physicians, Fellow; American Federation for Clinical Research; American Heart Association, Council for the Study of Arteriosclerosis; American Physiology Society; American Society for Clinical Investigation; American Society for Human Genetics; Association of American Physicians; British Cardiac Society (Corresponding Member); Deutsche Gesellschaft für Innere Medizin (Corresponding Member); Harvey Society (Honorary); Institute of Medicine, National Academy of Sciences; Institute of Society, Ethics and the Life Sciences (Associate Member); International Society of Cardiology; Medical Society of Sweden (Honorary); National Academy of Sciences; Peripatetic Club; Phi Beta Kappa; and Phi Kappa Phi.
Research Interests: Lipoproteins, lipid transport and metabolism; medical genetics, the cause and prevention of arteriosclerosis, health science, education and care systems.
Related professional activities:
Present—Member, Advisory Council of the American Center for Chinese Medicine; Life Associate Member, Intra-Science Research Foundation; Editorial Boards: American Journal of Medicine, Circulation, Circulation Research, Journal of Atherosclerosis.
Previous—Advisory Council on Research, New York State Heart Association; Chairman, Council on Arteriosclerosis, and member, Board of Directors and Central Committee, American Heart Association; American Society for Clinical Investigation, Council and Secretary-Treasurer; Bethesda Conferences Committee, American College of Cardiology; Cardiovascular Research Program Evaluation Committee, Veterans Administration.
Board of Directors, Foundation for Advanced Education in the Sciences; Cardiovascular Study Section, NIH; Executive Committee, Section of Atherosclerosis, International Society of Cardiology; NAS–NRC Committee on Fats, Food and Nutrition Board; Governing Board, National Research Council, NAS; Executive Committee, Assembly of Life Sciences, NAS; NAS–NRC Committee for the Study of Inborn Errors of Metabolism; Chairman and Member, Medical Board, NIH Clinical Center; Nutrition Research Advisory Committee, National Dairy Council; Stouffer Prize Committee; U.S. Coordinator, Problem Area 1, Prevention of Arteriosclerosis, U.S.-U.S.S.R. Cardiovascular Exchange Program;
Editorial Activities: American Physiology Society, Member and Chairman, Publications Committee; Editorial Boards, Journal of Clinical Investigation, Physiology in Medicine; Editorial and Advisory Board, Journal of Lipid Research.
Honors and Other Special Scientific Recognition:
Gold Medal Award, The American College of Cardiology, 1967.
The James F. Mitchell International Award for Heart and Vascular Research, 1968.
Department of Health, Education, and Welfare Superior Service Award, 1970, and Distinguished Service Award, 1971.
Modern Medicine Distinguished Achievement Award, 1971.

The McCollum Award (The American Society for Clinical Nutrition), 1971.
Election to the National Academy of Sciences, 1973.
Jimenez-Diaz Award (Madrid), 1974.
Intrascience Award, 1974.
La Modannina Prize for Science (Milan), 1975.
Honorary Lectureships:
American Swiss Foundation for Scientific Exchange University Lectures (Basel, Bern, Lausanne, Geneva, Zurich), 1964.
John Kent Lewis Memorial Lecture (Stanford), 1967.
Seventeenth Annual Convocation Lecture (The American College of Cardiology), 1968.
Third Bernard H. Pastor Memorial Lecture (University of Pennsylvania), 1968.
Marcus R. Caro Memorial Lecture (American Academy of Dermatology), 1968.
The Carl Herzog Guest Lecture (The American Dermatological Association, Inc.), 1969.
The Distinguished Lecture (Association of American Physicians), 1969.
Second George C. Griffith Scientific Lecture (Los Angeles County Heart Association), 1969.
Plenary Lecture, Deutsch Gesellschaft fur Klinische Chemi (Bonn), 1970.
St. Cyres Lecture (National Heart Hospital, London), 1970.
Wall Memorial Lecture (Children's Hospital of the District of Columbia), 1971.
Cardiac Society of Australia and New Zealand and National Heart Foundation Lecturer, 1971.
Alpha Omega Alpha Lecture and Visiting Professorship (Johns Hopkins Medical School), 1972.
Ernest William Goodpasture Lecture (Vanderbilt), 1972.
John C. Higgins Memorial Lecture (University of Oregon), 1972.
Harvey Lecture, 1973.
Samuel Bellet Memorial Lecture (Philadelphia), 1973.
The Jimenez-Diaz Lecture (Madrid), 1974.

SUMMARY REMARKS

Mr. FLOOD. You have some of your people here you would like us to know, I suppose.

Dr. FREDRICKSON. Yes, Mr. Chairman. Next to the durable figure at the end of the table [Mr. Miller], is Dr. Stetten, Deputy Director for Science; Mr. Leon Schwartz, the Associate Director for Administration of NIH is on my left; next to Mr. Schwartz is Dr. Lamont-Havers, Deputy Director of the NIH; and Mr. Norman D. Mansfield, Director of Financial Management.

Mr. FLOOD. Doctor, I see you have a pretty lengthy prepared statement. How do you want to handle that? Can we insert that in the record?

Dr. FREDRICKSON. I can paraphrase it and give you some of the highlights.

Mr. FLOOD. All right. Without objection, then, we will insert your statement in the record and have you comment on it or, if you prefer, paraphrase it.

Dr. FREDRICKSON. If I may.

Mr. FLOOD. Yes.

[The statement follows:]

Mr. Chairman and members of the committee, although I have testified before this committee in 1967 and 1968 as Director of the Heart Institute, this is my first opportunity to appear before you as Director of the National Institutes of Health, a post which I assumed on July 1.

This is also the first appearance of four new Institute Directors whom I should like to introduce:

Dr. Robert I. Levy became Director of the National Heart and Lung Institute in September. He joined the scientific staff of that Institute in 1963, shortly after receiving his MD degree from the Yale University Medical School, and for the

past 2 years he has been in charge of the Institute's research programs on arteriosclerosis as head of its Division of Heart and Vascular Diseases.

Dr. Richard M. Krause joined the NIH, as Director of the National Institute of Allergy and Infectious Diseases, on September 24. He is a graduate of Case Western Reserve University School of Medicine and comes to us from Rockefeller University where he has been professor and senior physician to the hospital since 1968. His previous associations with NIH include service as chairman of the Allergy and Immunology Study Section from 1966 to 1970 and as a member of NIAID's Infectious Disease Advisory Committee from 1970 to 1974.

Dr. David B. Scott returned to NIH on January 1 as Director of the National Institute of Dental Research. He first came to NIH in 1944, after receiving his DDS degree from the University of Maryland, and he was one of the 13 people who comprised the staff of NIDR when that Institute was created, by act of Congress, in 1948. He left in 1965 to become a professor in both the School of Dentistry and the School of Medicine of Western Reserve University; since 1969 he has been Dean of the School of Dentistry of Case Western Reserve University.

I expect that the appointment of Dr. Robert N. Butler as Director of the National Institute on Aging will shortly be announced. After receiving his MD degree from Columbia University, he served as a research psychiatrist with the National Institute of Mental Health, which was then part of NIH, from 1955 to 1962. He has since then been in private practice here in Washington and has written three books and many articles on the problems of aging. He served as a consultant to the Senate Special Committee on Aging and, pending completion of the formalities concerning his appointment, he is now serving as a consultant to the Institute. Dr. Greulich, who has been Acting Director since July, will testify on the budget request but Dr. Butler will, of course, be glad to answer any questions you may wish to put to him.

I found, on returning to NIH after a year's absence, that the morale of the staff is excellent and that both the intramural and extramural activities are being pursued with vigor, enthusiasm, and imagination. There are some problems such as the retention of highly skilled staff against an increasing gradient of compensation available in other Federal and private medical sectors, the need to define the mission of NIH and the boundaries of its activities in the light of increasing concern about the costs of health care, and the essentiality of sustaining the search for basic knowledge while increasing its clinical application toward prevention and cure of the many disease problems still to be solved.

One of the major problems is to define what needs to be done to insure an adequate linkage between biomedical research and the delivery of health services and to determine what role NIH can, and should, play in bridging the gap—for I have no doubt that a gap does exist. By this I do not mean that research results are lying on the shelf unused—this is, I know, a common allegation for which, however, there is simply no evidence. It is not a lag in development, but premature application of inadequately tested technology that is sometimes a problem in the linkage of research to health care. The continued success not only of NIH but of the biomedical research capability in this country which NIH sustains will, I think, depend on finding ways to meet the demonstrable needs of the health care system without, at the same time, damaging or subverting the research effort on which future progress in improving our health care capabilities so clearly depends. In its larger sense, it is not a problem which NIH can solve alone. The bridge across the translation gap will have to be built from both ends—and it will require consistent and innovative approaches at both ends. My main concern, as Director of NIH, is to consider what can best be done from the research end.

We are exploring what needs to be done to meet the needs for more clinical investigations, which are required to translate research done in the laboratory and with animals to medical problems of humans. There is increasing need for more carefully designed large-scale clinical trials to confirm the effectiveness of and demonstrate new diagnostic or therapeutic procedures.

Another aspect of the translation gap is perceived as the problem of the dissemination of research results to the health service community. The better dissemination of research results is a matter that is not only of great concern in the Congress and elsewhere but that bears directly on the definition of the mission of NIH and the evaluation of the role it must play in furthering the health of the American people.

Because of its immediate and continuing importance, I appointed, last September, a task force of knowledgeable scientists—under the chairman ship of

Mr. Whaley, the Associate Director for Communications—to design, implement, and monitor our communications efforts. A subcommittee of professionals on this task force, chaired by Dr. Seal, the Scientific Director of the Allergy and Infectiious Disease Institute, has accepted responsibility for a continuous review of research results to select those that are of potential importance to the practicing health professional and to assess their clinical significance. In addition, we have held informal consultation with outside communications experts and we have launched a series of national workshops to review existing means for disseminating research information and to recommend improvements and new approaches. These arrangements will, I think, provide a sound basis for the orderly development of this program, for the continuing evaluation of its effectiveness, and for the identification of unmet needs.

At last year's hearings, Dr. Lamont-Havers, who was then Acting Director of NIH, described various kinds of research results and identified groups to whom each type is of potential use. In this connection, he mentioned the ever-increasing uses for continuing eeducation of health practitioners. He affirmed NIH's determination to take all reasonable and feasible steps to make usable information as easily and readily available to them as possible. We have given much thought to how this can best be done and believe that one effective approach is to improve systems for "instant consultation" with physicians in need of information and advice. Such a system at the University of Alabama Medical Center at Birmingham—started in 1969 under the aegis of the regional medical program but now supported by State funds—is now used by three-quarters of the Alabama physicians outside the Birmingham area who each week make some 500 inquiries that are answered by the appropriate expert among the Center's 150 faculty members. We believe that this pattern can be followed with equal success in other areas and that some of the categorical research centers that NIH has established at major medical centers in various parts of the country provide a good foundation on which such a system can be built.

To test the effectiveness service, established last year at the University of Wisconsin, so that it can provide a toll-free telephonic consultation service for physicians throughout the State, on all disease problems. The success of this pilot project will, of course, depend—as it did in Alabama—on the enthusiasm and dilligence of the professional staff in the Madison Medical Center. I have full confidence in their determination and ability to make it work and I expect that their efforts—and those of the dedicated group in Alabama—will set a precedent that other medical centers, with the assistance and encouragement of NIH, will be willing to follow. At the request of both the Alabama and the Wisconsin groups, we will organize a back-up service, drawing on our experienced professional scientific staff in Bethesda, to deal with questions that the local faculty refers to us. I believe that direct links, between community physicians and their State or regional medical centers and between the centers and the NIH staff, dealing with real problems, as they arise, is probably the most effective way of bridging the gap between those at the research frontier and those at the bedside.

In order to reach larger groups of health practitioners with more comprehensive reviews of the state of the art in various fields of interest to them, we will, initially, use the existing State and regional special television networks that now link hospitals and medical centers in Indiana, South Carolina, the Houston area, the Dartmouth-University of Vermont area, the six-State WICHE (Western Interstate Commission for Higher Education) region, and the VA hospitals in Appalachia. The plan is to present regularly scheduled seminars, lectures, demonstrations, and other professionally oriented programs. The content of these programs must be of the highest quality and must be carefully tailored to the needs of an audience of busy practitioners.

This takes time and is apt to be expensive but we will move as rapidly as talent and funds will allow. We expect that the audience for these programs can be substantially enlarged, and at a lower unit cost, through the use of the communications technology satellite which was launched on January 17. NIH, through the Lister Hill Center of the National Library of Medicine—and in cooperation with the Health Resources Administration—is participating in the CTS project which, when it becomes operative next autumn, will provide two-way links between stations in Bethesda, Seattle, Fairbanks, Boise, Helena, Gainesville (Florida) and an NLM mobile unit. As these stations will be able to transmit, as well as receive, discussion programs will be possible. We also intend to make these facilities available, in time allocated to NIH, to professional

societies which can, and must, play a more active role in the dissemination of information to the practicing community.

A report on the status of the dissemination program has been submitted. A number of other activities are described therein, includuing the preparation of a monthly research review to be published in an established journal and an increased output of health information publications and audio-visual materials.

In order to assess the receptivity of those in the health-care community to the various modes of communication, we are making arrangements with the American Academy of Family Practice to conduct a survey among its members on the acceptability and effectiveness of the NIH dissemination activities.

As I have already mentioned, we are collaborating with the Health Resources Administration on the CTS project. Information on NIH research has been regularly supplied to the new Professional Standards Review Organizations since last April, we are supplying video-taped lectures to VA hospitals, and we are working with the Bureau of Health Education, in the Center for Disease Control, on improving health education for the public. In planning our dissemination program, we are alert to the mission of the Health Resources Administration in the education of health professionals, the responsibility of the Professional Standards Review Organizations for continuing education, and the expanded role of the new Bureau of Health Education for informing the public.

Another aspect of cooperation and coordination that is of concern to this committee, as it is to me, is between the various components of NIH itself. All of us recognize, I think that the categorical organization of NIH is efficient but is sometimes at odds with the natural distribution of labor among scientists converging, from many directions, on the solution of disease problems. The research scientist tackles biomedical problems from the point-of-view of the scientific disciplines in which he has been trained. A virologist, for example, is interested in identifying viruses and discovering what diseases they cause; his mental processes are not fenced in by the specific disease mission of the Institute that pays his salary or awards him a grant. It is therefore not surprising that most of the initial work on the virology of cancer was done by scientists supported by the Allergy Institute which has always been deeply involved in the study of viruses. The work of good scientists, in which intuition and curiosity must play a major role, often leads them into fields far removed from their own pastures. A recent example, with which you are probably familiar, was the development of the rubella vaccine which was properly the task of the Allergy Institute (which is responsible for infectious diseases) or, possibly, the Child Health Institute (which worries about the diseases of childhood and pregnant mothers)—but the main work, the research that provided the "breakthrough" necessary for the development of the vaccine was done, independently, by intramural scientists working in the Neurology Institute and in the Division of Biologics Standards, which was then part of NIH.

The work of several Institutes is often relevant to a particular disease or medical problem—or, to put it the other way round, a particular disease often has aspects that fall within the purview of several Institutes. This is particularly true for such areas of research as diabetes, cystic fibrosis, and most of the respiratory diseases. There is a limit, I believe, to the validity of concerns that a lack of coordination is retarding movement in certain diseases or that this is due to lack of management procedures that are effective for achieving engineering feats. Yet we cannot afford to ignore possibly better stimulants to creativity and the interactive acceleration of research. We will be most attentive to the requests in the recent report of the Diabetes Commission and to other innovative ideas for creating more effective linkages between different laboratories and institutions working on common problems.

The budget request now before you includes $21.7 million for the first phase of the construction of the addition to the Clinical Center on the Bethesda campus. The proposed extension, for which the plans have been completed, is an ambulatory care research facility primarily intended for clinical research involving out patients who do not have to be hospitalized. This facility will serve at least eight of the institutes and is designed to meet two critical needs. The first is to accommodate a shift in clinical practice toward out-patient treatment and in clinical research toward the study of both normal as well as diseased populations as out patients. Impressive savings in the mounting costs of health care and in clinical investigation can be realized. No less important is the opportunity to extend knowledge about the development of disease, its diagnosis and treatment, in subjects living their lives at home or outside the artificial conditions of the

hospital. Many clinical interventions must now be tested for their efficacy, safety and cost effectiveness in large numbers of subjects. Most important of all is the increased capability for research on the prevention of disease, the ultimate direction of all medical research. There has been a commendable shortening of hospitalization over the past several decades.

The continuation of this trend has been made possible by numerous technical advances and has also, no doubt, been accelerated, in recent years, by the sharply rising cost of bed care. Many of the diagnostic procedures, for which people used to be hospitalized, can now be done—with greater convenience for the patient and at far less cost—on an out-patient basis. Similarly, it is now not only possible but preferable to give ambulatory care to patients in the early stages of chronic or degenerative diseases, during periods of remission, and in the recuperative phase of an acute illness. For research patients, the need for ambulatory care facilities has grown even more rapidly as the result of the expansion of research on normal human subjects and on illnesses, disabilities or abnormalities that do not require hospitalization but that do require the use of the sophisticated equipment and facilities of a hospital or large clinic. This is true of clinical research in general but is particularly true of the newer Institutes—Child Health, Eye and Aging—whose research patients, for the most part, need not be confined to bed. As the result of all these factors, the Clinical Center now handles about 77,000 out-patient visits a year. This is an increase of 50 percent over 1971 and the figure would be very much higher if the present facilities were not now at capacity use. The number is already too high, leading to inconveniences for patients and some sacrifices of their dignity, privacy and comfort.

The new facility will eventually accommodate over 190,000 out-patient visits a year—a capacity that will make it possible to expand clinical observations and trials and optimally to meet the foreseeable needs of future clinical research programs. In order to streamline the handling of outpatients, various technical services now located in scattered parts of the Clinical Center will be brought together in the new structure.

The other major, and even more urgent, need for which the new structure is required is to permit essential modernization and renovation of the existing structure. The Clinical Center was planned in 1948 and opened 22 years ago. What was once the most modern of American hospitals has suffered obsolescence in the succeeding years of great technological change. Facilities for certain types of surgery and intensive care are falling seriously below standard. Space for clinical pathology, diagnostic x-ray and other new but essential diagnostic services is woefully inadequate. For purposes of renovation to the present Clinical Center $8 million is included in the total estimated cost for the Ambulatory Care Research Facility. The proposed expansion and modernization of the Clinical Center is absolutely necessary if NIH is to remain at the forefront of the research activities required to continue its mission of providing the scientific basis for improving the health of the American people.

This year's budget makes a conscious and somewhat overdue effort to maintain capabilities and pursue selected important opportunities in the overall biomedical research effort. Since 1971, the year before the Cancer Conquest program was launched, the appropriation for the Cancer Institute has increased from $233 million to $762 million in 1976. That has been an appropriate surge of support for research on this disease problem, clearly identified—and, I think, properly so—as a national initiative. In 1971, funds for the Cancer Institute represented 14 percent of the total NIH appropriation; in 1975 and 1976 they represented 33 percent. The amount allocated to cancer in the fiscal year 1977 budget is 32 percent of the NIH total and to this must be added a substantial share of the separate appropriation for the construction of the Ambulatory Care Research Facility which will, proportionately, be of the greatest assistance to the Cancer Institute in carrying out its important mission.

The fiscal year 1977 budget request for NIH is just over $2,165 million which is $137 million less than the fiscal year 1976 appropriations that were passed over the President's veto last month. This decrease is due to the fact that the fiscal year 1977 budget was constructed on a lower base, before the fiscal year 1976 appropriations were enacted; it does not reflect $112.5 million of the fiscal year 1976 Congressional increases for the Cancer, Health, Child Health, and Aging Institutes, $43 million for General Research Support Grants, and $51 million in nonrecurring construction funds.

For the other NIH components, there are increases totalling $42 million which represent our best professional judgment on relative opportunities and needs. This amount includes $6.8 million for the National Institute on Aging which, with an appropriation of $26.2 million, will be able to mount a reasonable research program that will provide a sound beginning for the discharge of the mission for which it was created. There is an increase of $8.4 million for the Environmental Health Institute which has the unique responsibility, within the NIH family, for conducting research on a seemingly endless array of natural and man-made agents that assault our bodies and seem to cause a bewildering variety of diseases and disabilities. Many of these agents have not yet been identified and their relation to many diseases is still unsuspected or in doubt but we are clearly at the frontier of a new field in medical research that may prove as fruitful as the discovery, less than a century ago, that bacteria are a cause of disease. NIH must not shirk its responsibility for exploring this field but even with this increase the Environmental Health Institute will, in terms of budget, remain the smallest of the Institutes, other than Aging.

In order to achieve a better balance among the other programs, to correct serious deficiencies, and to meet specific urgent needs, there are increases of $8.5 million for the Allergy Institute, $6 million for the General Medical Sciences Institute, $1.8 million for the Neurology Institute, and $1 million for the Arthritis Institute.

The budget request for the Fogarty International Center includes an increase of $1.8 million for its scholars-in-residence and fellowship programs, which are making significant contributions to the international exchange of information by giving outstanding foreign scientists an opportunity to work and study in this country and outstanding American scientists an opportunity to work and study abroad. For the Library of Medicine, an increase of $6 million is requested, part of which will enable it to take full advantage of its participation in the Communications Technology Satellite project.

For research training, the budget request of $108.5 million of which $34.1 million is for the training grant programs that have been superseded by the fellowships awarded under the National Research Training Act. Although this Act has expired, we still have authority for the old training and fellowship programs that are being phased out. Funds totalling $73.2 million for fellowships under the National Research Training Act are included in the budget submission in the expectation that the renewal legislation, which is now in conference, will be enacted before this committee acts on the fiscal year 1977 appropriation. The amount requested for these new fellowships represents an increase of $19.5 million which will provide for about 900 additional fellowships.

I am sure that the members of this committee share my hope that the effectiveness of NIH will continue to grow, that this country will march forward to greater achievements in research, and that the expectations of the American people for a longer, healthier life will thereby be progressively fulfilled. That is the purpose for which the funds in this budget are requested.

SUMMARY REMARKS

Dr. FREDRICKSON. This is the first time since 1968 that I have been privileged to testify before this committee. As Director of the Heart Institute, I was here in 1967 and 1968. I assumed the position of Director of the National Institutes of Health last July 1.

NEW INSTITUTE DIRECTORS

I am pleased that for the first time in some time we have a full complement of Institute Directors, and during the course of these hearings it will be a pleasure to introduce to you Directors Robert I. Levy, Richard M. Krause, and David B. Scott, who are the new Directors of the Heart and Lung, the Allergy and the Dental Institutes, respectively. Their curriculums vitae and qualifications, which are excellent, will be presented to you at the time they appear before you.

Also, shortly to be announced is the appointment of Dr. Robert N. Butler as the first Director of the new Institute on Aging. Dr. Butler

is a psychiatrist who graduated from Columbia, was in the National Institute of Mental Health here and is a practicing psychiatrist in this city, but who has had much experience and long service on a number of committees relative to research and other aspects of the aging problem. We are very privileged that he will shortly be the Director. During these hearings Dr. Richard Greulich, the Deputy Director of the Institute, will testify before you, but you can hear from Dr. Butler, should you so desire.

PERSONNEL

On returning to NIH I was pleased to find its morale in what I considered to be very good shape. It is still a vigorous and active organization. There are some problems, but they are not insurmountable.

I am concerned, among other things, however, that we still have problems in maintaining very highly skilled technical personnel in the face of some high gradients of compensation now both in other Federal medical sectors and certainly in the private area.

We have been working hard to continue to prune and reshape the definition of NIH with regard to its functions in relationship to increasing costs of health care and the essentiality for seeing that the quality of health care continues to improve.

CLINICAL TRIALS

We have been particularly concerned also with the role of the NIH in linking its biomedical research mission to the delivery of health care. We have been searching hard for gaps that may exist in the translation of our research activities and to assure ourselves that we, at our end, can establish better mechanisms for making sure that there is no translation lag. One of the things that we are also particularly concerned about is our ability to handle effectively the increasing load of clinical investigations, large-scale clinical trials in particular, which is, in part, the result of two decades of greatly increased biomedical research. More developments are being brought up for translation and that has a particular bearing on the problem of making sure that interventions don't get prematurely into the health care delivery system which may do more harm than good and could add remarkably to the cost.

DISSEMINATION OF RESEARCH RESULTS

Another aspect of the translation gap is to make sure that the results of research are properly disseminated, particularly to the professional health service community, but also, through them, to the public. We have been devising ways to improve our own participation in this important activity.

We have established a task force under the chairmanship of Mr. Whaley, Association Director for Communications. It is made up of scientists from each of the Institutes and has a panel, headed by the very able scientific Director of the Allergy Institute, one of whose functions is to pick up, on a cyclical basis, those aspects of research development that should be featured in attempting to bring results

in a continuous and understandable way to the practicing health professional.

We have also been meeting informally with consultants from the communications industry. We have launched a series of workshops to bring up to date our knowledge about how we can improve dissemination methods by current techniques in communication. We are particularly aware of the need to establish a one-to-one relationship between the health practitioners and those who can advise them on new methods and procedures.

One of the devices that we believe is going to be effective is a system developed at the University of Alabama, which makes the members of the medical faculty available through a telephone switchboard to all the practitioners in that State, nearly two-thirds of whom have been using the system, for contact and consulation. This has been a very effective system. We have in various parts of this country several kinds of centers for advanced work in a variety of diseases. One of these is the cancer centers. We have recently been negotiating with the Cancer Center at the University of Wisconsin, which has an on-line communications system of this sort. They would be very much interested in broadening it to cover all health problems. So we are going to see that they are supplied with enough resources to do that. We at NIH will also back up both the Wisconsin and the Alabama systems by consultations with physicians referred to us by the medical faculties. This will be an important experiment to see if we can improve and update the information available to practitioners with regard to all kinds of medical problems they confront in their practices.

We are also going to increase our activities with regard to linkages between certain hospitals and medical centers through television networks which we now have available to us in several areas. Our plan is to present regularly scheduled seminars and lectures and other professionally oriented programs, carefully designed to be of the highest quality. We shall eventually be able to enlarge our audience through the use of the communications technology satellite that was launched January 17. NIH, through the Lister Hill Center of the National Library of Medicine, and in cooperation with the Health Resources Administration, is going to participate in this project, which, when it becomes operative, will help link NIH stations in Bethesda and some communities scattered throughout the United States. Some of these will actually permit two-way communication so we can have a discussion with practitioners such as is now possible through the existing linkage between Alaska and the Northwestern States.

We are eager to know the effect of these programs on practicing communities. We are therefore making arrangements with the American Academy of Family Practice, for example, to conduct a survey among its members on the acceptability and the effectiveness of these dissemination activities.

In addition to these, we are supplying to the VA regular videotape lectures; we are working with the new Bureau of Health Education in CDC to assist them in their attempts to improve health education for the public; and we are working with the other agencies in the Public Health Service in this regard.

COORDINATION OF INSTITUTES

Another of the preoccupations that I have had since returning, Mr. Chairman, is to see how we can improve the coordination and relationship of the several Institutes of the NIH with regard to disease problems that are crosscutting, which involve work in a variety of Institutes, and the need to assure that these results are brought back together and coordinated and resynthesized as frequently as possible in order to be sure we keep the movement on a particular disease forward and as rapidly as possible.

In my own view, Mr. Chairman, there has not been any real lag in taking research results off the shelf. I think the real problem, and we have to face that, is that sometimes things get prematurely into the health care system, before they have been adequately evaluated. Nevertheless, it is incumbent upon us to be very careful that we use all the ingenuity and care in management of these crosscutting programs, to be sure we don't lose momentum or opportunities to take advantage of results and findings in one field, to bring them to bear on a whole variety of diseases, particularly diseases like diabetes, multiple sclerosis, cystic fibrosis and many others, the nature of which still remain so much a secret and for which the source of the key information is still to be determined.

AMBULATORY CARE RESEARCH FACILITY

Mr. Chairman, the budget request that is now before you includes $21.7 million for the first phase of the construction of an addition to the Clinical Center on the Bethesda campus. This proposed extension, for which the plans have been completed, is an ambulatory care research facility, primarily intended for clinical research involving outpatients who do not have to be hospitalized. This facility will serve at least eight of our Institutes. It is designed to meet two very critical needs. The first is to accommodate a shift in the nature of clinical research that is occurring not only in Bethesda but throughout this country and the world. It is part of the shift in clinical practice to get people out of the hospital as rapidly as possible and keep them out as long as is possible because of extraordinary cost that is involved in institutionalization and in hospitalization. Impressive savings can be realized in this way.

From the standpoint of research, it is particularly desirable and necessary today to study rather large numbers of people while they are living in their community and their typical ways of life—especially in research designed to develop means of better preventing a large number of diseases before they actually occur. So that there is an essential need for increasing our capability for doing outpatient research.

At the present time we are at the limit of the number of outpatients that we can handle in the Clinical Center at NIH. We are now seeing about 77,000 outpatients a year. That is an increase of about 50 percent since 1971. The number that we will see in years to come is projected to increase very rapidly, provided we can accommodate them in new facilities. At present we are seeing all the outpatients, we can. In fact, it has been necessary for us to expose them to some discomfort

and, at times, to some loss to dignity and privacy, because we are working in such crowded conditions.

The new ambulatory care research facility that has been designed will eventually allow us to accommodate up to 190,000 such visits per year, in the future when NIH realizes its total potential with regard to this important aspect of ambulatory care research. It will allow us to streamline the manner in which these patients are seen and centralize services provided to them which are now scattered throughout the very large building. The loss of efficiency in the use of some of our diagnostic services and the loss of time to patients and to staff is considerable.

MODERNIZATION OF CLINICAL CENTER

Certainly no less urgent than this, and perhaps even slightly more important, is the need for the present structure to be modernized and renovated. The Clinical Center was planned in 1948 and it was opened 22 years ago. At that time it was one of the most modern of all American hospitals. But it has suffered considerable obsolescence, I suppose much as the result of the discoveries that NIH has fostered which have revolutionized so much of hospital design and utilization in the United States. But now at NIH the facilities for certain types of surgery and for intensive care—particularly in cancer surgery and eye surgery—are falling very seriously and are now well below standard. Space for clinical pathology, to do so many diagnostic tests, is woefully inadequate; also for diagnostic X-ray, in which new techniques are requiring more and more space for bulky equipment, and for other essential diagnostic services, the facilities are now really completely inadequate.

For purposes of renovation in the existing Clinical Center, $8 million is included in the total estimated cost for the ambulatory care research facility. The proposed expansion and modernization of the Clinical Center, I believe, Mr. Chairman, is absolutely necessary if the NIH is to remain at the forefront of the research activities required to continue its mission in providing the scientific basis for improving the quality of the health of Americans.

BUDGET REQUEST

This year's budget that is before you, Mr. Chairman, makes a conscientious and somewhat overdue effort, we think, to maintain capabilities and to pursue certain selected and important opportunities in the overall biomedical research effort. We noted last Friday, in testimony before you, that in 1971, the year before the cancer conquest program was launched, the appropriation for the Cancer Institute was $233 million. This has increased to $762 million in 1976. I think that has been an appropriate surge in support of research on this disease problem, which I think is clearly and quite properly identified as a national initiative.

In 1971 funds for the Cancer Institute represented about 14 percent of the total NIH budget. Last year they represented 33 percent, and in the 1977 budget, which you have before you, they represent 32 percent and that does not include a substantial share of the cost of construction of the new ambulatory care research facility, of which they will probably be the largest single user.

The fiscal year 1977 budget request for NIH is just over $2.165 billion, and that is $137 million less than the fiscal year 1976 appropriation that was passed over the President's veto last month. However, this decrease is due to the fact that the fiscal year 1977 budget was constructed on a lower base, the 1976 operating level in effect before the 1976 appropriation was enacted. It therefore does not reflect $112.5 million of the fiscal 1976 congressional increases for Cancer, Heart, Child Health and the Aging Institutes; the inclusion of some $43 million for the general research support grants, now called biomedical research support grants; and $51 million in nonrecurring construction funds.

For some of the NIH components, the 1977 budget contains increases that total $42 million, and these represent our best professional judgment on relative opportunities and needs. This amount includes $6.8 million for the National Institute on Aging, which is just beginning to get started, and will bring its appropriation up to $26.2 million, with which I think it can mount a reasonable approach to the problems of aging and the aged and give this new mission a reasonable beginning.

There is also an increase of $8.4 million for the Environmental Health Institute, which, as you know, has a rather unique responsibility today. We are on the threshhold of a whole new source of disease problems resulting from environmental factors which is, I suppose, about as important today as was the discovery of the relationship of bacteria to disease almost a century ago. NIH wants to fully accept its responsibility for biomedical research in this field, but I should note that even with this increase in the budget, the Environmental Health Institute will, in terms of budget, still remain the smallest of the Institutes, other than Aging.

There are also increases in this budget of $8.5 million for the Allergy Institute, $6 million for General Medical Sciences Institute, and $1.8 million for the Neurology Institute, and $1 million for the Arthritis Institute.

The budget request for Fogarty International Center includes an increase of $1.8 million for its scholars-in-residence and fellowship programs. For the National Library of Medicine there is an increase of $6 million, part of which will enable it to take full advantage of its participation in this communications satellite technology project.

RESEARCH TRAINING

For research training, the budget request is $108.5 million, of which $34.1 million is for the training grant programs that have been superseded by the fellowship awarded under the National Research Training Act of 1975. As you know, that act has expired, but we still have authority for the old training and fellowship programs that are being gradually phased out. Funds totaling $73.2 million for fellowships under the National Research Training Act are included in this budget submission in the expectation that the renewal legislation, which is now in conference, will be enacted before this committee will act on the 1977 appropriation.

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PURPOSE OF FUNDS

I am sure, Mr. Chairman, that the members of this committee share my hope that the effectiveness of NIH will continue to grow and that this country will move forward to continuing greater achievements in health and in research, and that the expectations of the American people for longer healthier life will thereby be progressively fulfilled; and this is the purpose for which the funds in this budget are requested.

NATIONAL MEDICAL RESEARCH EFFORT

Mr. FLOOD. Now, Doctor, in order to put this NIH request in the proper perspective, can you tell us what the total level of expenditures is going to be for 1977 for biomedical research in the United States, and what percentage of that total is going to be supported by NIH? Last year we were told it would be about $4 billion.

Dr. FREDRICKSON. $4 billion. I think that this budget will continue to allow the Federal Government to support about two-thirds of the biomedical research effort. This NIH budget will be two-thirds of the Federal effort, and that will be about two-thirds of the total biomedical research effort in the United States.

Mr. FLOOD. You don't have a figure off the top of your head?

Dr. FREDRICKSON. Yes; if we add to the NIH budget approximately one-half, it would bring the amount from Federal sources to about $3 billion, and to that we add $1 billion, which is the continuing figure for the contribution of industry, largely the pharmaceutical industry, we will get at a figure of $4 billion.

Mr. FLOOD. All right. With this funding level that you have just mentioned, at what level of capacity would you say the whole biomedical research industry will operate in fiscal 1977? 100 percent, 90 percent, what?

Dr. FREDRICKSON. Its capacity, of course, is variable.

Mr. FLOOD. That is the understatement of the day. That is right; yes.

Dr. FREDRICKSON. I would say it will operate fairly near the existing capacity that it has today, Mr. Chairman, because as elements of the program are no longer maintained in the system they fail to remain operative.

SINGLE NIH APPROPRIATION

Mr. FLOOD. I understand. This budget before us proposes a single appropriation for NIH. What are the advantages of this type of funding consolidation?

Dr. FREDRICKSON. I think the administration has been desirous of attempting this single appropriation instrument as a way of simplifying its evaluation process, Mr. Chairman.

But you will see that for our purposes of evaluation, and certainly for our presentation to the Congress, we have retained the complete breakdown and display along Institute lines that we find so valuable for program management, and you for evaluation of the appropriation.

Mr. FLOOD. Would there be some advantage here for any merging of research opportunities?

Dr. FREDRICKSON. I think that in dealing with the overall figure within which we have to work we do take into account, in making allocations to each of the Institutes and Divisions, such opportunities, and attempt to make our distribution that way.

Mr. FLOOD. Some people have told us that the Director of NIH must have greater flexibility in managing and allocating all the resources within NIH. Will this single appropriation give you that flexibility?

Dr. FREDRICKSON. It would possibly, if it were treated as a single appropriation, provide a certain amount of increased flexibility or opportunity for reprograming. But most of that opportunity and flexibility we still enjoy under the existing system by negotiating with the Institutes at the time that the total budget is put together, element by element.

Mr. FLOOD. Doctor, are you proposing this type of appropriation consolidation in order to give the freedom of reprograming all of this money without notifying Congress?

Dr. FREDRICKSON. The answer is unequivocally no, sir.

Mr. FLOOD. You know our position here. This is the Appropriations Committee. We don't want reprogramming funds within an appropriation without notifying and obtaining congressional approval. I ask you that question out of an abundance of caution, if you know what I mean.

Dr. FREDRICKSON. Yes; I understand what you mean, Mr. Chairman. That certainly is not the intent.

RESPONSIBILITY FOR BUDGET ALLOCATIONS

Mr. FLOOD. Now, in your statement, you state: "The increases represent our best professional judgment." Well, now, does that mean that you have had a freer hand in the allocation of this budget allowance?

Dr. FREDRICKSON. We have proceeded this year, as I believe in years past, Mr. Chairman, to operate within the constraints of a total budget to the best of our ability to judge where we would place emphasis.

Mr. FLOOD. As I understand it, what you are saying is that where we see any increases, you have made the increases; and where we see any decreases, this was also your decision and not the decision of OMB. This is very interesting. What in the world are you going to do if you don't have OMB to kick around?

Dr. FREDRICKSON. Actually, Mr. Chairman, the increases and decreases that you see in comparing the 1977 budget to the 1976 appropriation are the result of that appropriation. We made our recommendations on a different base. These increases are shown in a set of tables with regard to our estimate to the Department, for example. These increases are larger and are somewhat differently distributed from the increases shown by a comparison with the recently enacted 1976 appropriations.

Mr. FLOOD. But the increases, wherever we see any increases, they were made by you, and the decreases were made by you, isn't that about it? Not OMB. The answer is yes, isn't it?

Dr. FREDRICKSON. The distribution is essentially ours, Mr. Chairman.

Mr. FLOOD. We have a volunteer.

Mr. MILLER. I am not entirely sure I understand the question. I am sure Dr. Frederickson doesn't, either. I think Dr. Frederickson would agree that the distribution of the research dollars does match his priorities.

I think, however, our action took place after it was determined how much of the health dollar was going to go for research.

BUDGET FOR CANCER AND HEART DISEASE

Mr. FLOOD. All right. In the past years we talked about various pressures coming into play in setting national priorities in the allocation of very scarce resources. One of the prime determinants in the allocating of health resources has always been the scientist's concern about any given disease, no matter what it may be.

Now, keeping in mind what I just said as the premise, your budget reduces the funding for the Cancer and Heart Institutes. Is society no longer concerned about these diseases, or is there some other reason for this reduction?

Dr. FREDRICKSON. I think society is still very much concerned about cancer and heart disease, and so are we, Mr. Chairman. It is simply that within the total budget constraints, we also felt that we had to be sure that our capabilities in certain other key areas were not irrevocably lost by what in some Institutes was a steady decline of purchasing power.

Mr. FLOOD. I had an idea you might say that. That leads me to ask you this: You realize that every Member of Congress is, has been, and will continue to be swamped with letters urging that we add several hundred million dollars to the Cancer Institute in order to find a quick cure for cancer. All right. What do you suggest we tell them?

Dr. FREDRICKSON. I think, again, Mr. Chairman, that the important asspect of this is that we are now supporting vigorously an increased assault upon cancer and have been for the last several years. The apparent leveling out of the budget for that Institute does represent our attempt to redress what, in our view, are certain needed imbalances within the total of the biomedical research program.

Mr. FLOOD. I just asked you, what are the Members going to say? You don't want them to quote what you just said, do you?

Dr. FREDRICKSON. If I might offer you an additional argument?

Mr. FLOOD. Very well.

Dr. FREDRICKSON. Particularly in cancer, but indeed for many of the serious chronic diseases that we face today, we really are not at the stage of programing an engineering feat. Curing cancer, even discovering its cause, is not the same as going to the Moon. That means that we don't know where the secret of cancer or of some heart diseases or of diabetes will come from. It may come from research that is quite fundamental, exploratory, relatively undifferentiated and not at the moment identified with that particular disease at all.

LOCI OF CANCER RESEARCH

Mr. FLOOD. Are you saying that such extensive biological research in connection with the whole spectrum of diseases is what might help cancer most?

Dr. FREDRICKSON. Yes. Single thrusts in research that may relate to the control of biochemical events in the cell, of replication of the cell, a whole host of examples could be given, because it may be——

Mr. FLOOD. You say things like that would contribute to a cancer cure?

Dr. FREDRICKSON. Indeed they will, because there may lie the whole secret which we will eventually be able to exploit and develop into cures and preventions.

PRESIDENT'S BIOMEDICAL RESEARCH PANEL

Mr. FLOOD. Does this 1977 budget for NIH reflect any recommendations from the President's Biomedical Research Panel?

Dr. FREDRICKSON. Not yet, Mr. Chairman, because that Panel has not yet issued its report. It is due next month.

Mr. FLOOD. What is the status of that report, the President's Biomedical Research Panel? Are you at the present time applying their recommendations to any of the NIH programs?

Dr. FREDRICKSON. Not yet, because they have not issued their report.

COOPERATION WITH PROFESSIONAL SOCIETIES

Mr. FLOOD. In your opening statement and in your comments on the opening statement, you devoted a large part of the time to the dissemination of research results. I am glad you did that, and we are glad to see that you are making some progress in that area. We have talked about this for a couple of years. However, you spoke about medical centers and the practicing physicians being linked up with a lot of expensive hardware, I guess. It appears to us that you didn't adequately emphasize one particular group, the professional associations. We didn't hear much about that. Why is that? We understand that they are pretty much concerned about the continuing education of their members.

Dr. FREDRICKSON. Yes; they are, and it is our desire to work with them as groups within the practicing communities. I think they can be very useful.

Mr. FLOOD. Professional associations, societies.

Dr. FREDRICKSON. Yes, Societies of professionals as well as working with professional societies that include lay people with an interest in specific diseases.

Mr. FLOOD. Would you describe that as a comparatively inexpensive mechanism for communicating new knowledge?

Dr. FREDRICKSON. I think it is. I think it can be relatively inexpensive.

Mr. FLOOD. You also said you are making arrangements with the American Association of Family Practice to conduct a survey of the practicing physicians. In order to determine the effectiveness of this NIH dissemination of activities and information and so on. When do you think you are going to finish that survey?

Dr. FREDRICKSON. That will be finished sometime this year, sir, but I can't give you a more specific figure.

Mr. FLOOD. This calendar year?

Dr. FREDRICKSON. I hope so, this calendar year.

COOPERATION WITH FEDERAL AGENCIES

Mr. FLOOD. You also say in order to successfully disseminate all this information to the practicing physicians and to the general public, I would hope, cooperation with other Federal agencies is important. I couldn't have said that one better myself.

Well, would you assess that cooperation? Is there improvement?

Dr. FREDRICKSON. Cooperation is growing continually among the agencies in this regard, Mr. Chairman.

Mr. FLOOD. Where is the improvement needed?

Dr. FREDRICKSON. The improvement is needed in several areas. First, to assign, clearly, the various tasks that should be performed by different agencies, and this has not always been the case in the past.

For example, when assigning to one agency primary responsibility for getting to the public, it is probable that another agency will have to see that the health professionals in that same area are also prepared for the dissemination of such information to the people who will be their patients.

It is in this latter role that I think NIH can be particularly helpful, because its interface is more with the professional community and with the places where physicians are taught and where research is conducted than with the general community, per se.

INTRAMURAL RESEARCH

Mr. FLOOD. Now, since you had a much freer hand in building this budget, how would you characterize the support for the intramural research program? From everything we have heard about it—and we have heard a great deal—this program is internationally acclaimed, and has contributed significantly to curing disease.

Dr. FREDRICKSON. We think this is an excellent program, Mr. Chairman. It has been in the past, and I think it continues to be one. We continue to support it at about the same level.

Mr. FLOOD. What about funding?

Dr. FREDRICKSON. The funding for it is about the same in terms of total percentage.

Mr. FLOOD. Yes; in spite of everything you are saying and in spite of everything I have said, do you think it is adequately funded?

Dr. FREDRICKSON. I think it is adequately funded, Mr. Chairman. When I say the funds are the same, I mean the same percentage of the total budget. But of course we have added one very important item this year, that is the construction of the ambulatory care research facility.

POSITIONS

Mr. FLOOD. From the justification material before us, it appears that you did not receive authority to fill all of the positions that Congress added in fiscal 1976 for NIH. Is that right?

Dr. FREDRICKSON. That is correct, Mr. Chairman. We have requested such authorization.

Mr. FLOOD. And you didn't get it?

Dr. FREDRICKSON. We have not yet received it.

Mr. FLOOD. How many did you receive authorization to fill; any?

Mr. MILLER. The authorization from the President was at the level of the budget that was presented to you.

Mr. FLOOD. What is the impact of not getting the additional slots?

Mr. MILLER. We expect to be able to authorize the National Institutes of Health to fill all of the positions in the appropriation. As you know, we have informed the committee that there will be no rescissions sent to the Congress of items in H.R. 8069. We assume that that discussion includes the authority to fill all of the positions in the bill. We haven't got our i's dotted or t's crossed with OMB on that, but that is what we expect the decision to be.

MANPOWER MANAGEMENT PROGRAM

Mr. FLOOD. While we are on the subject of additional positions, we have a little problem here. Doctor, last year we had all types of people telling us that NIH needed more personnel. Believe me, they sat here and were very emotional about it. Do the NIH Institutes have a manpower management program which will provide us with some quantitative data regarding this business of your specific manpower needs?

Mr. SCHWARTZ. Yes, sir. We are undertaking what is known as a zero-base analysis, going right back to ground zero, estimating our manpower on the basis of the productivity indices. This will be available.

Mr. FLOOD. When will all the institutes at NIH incorporate this procedure?

Mr. SCHWARTZ. It will certainly be incorporated in the fiscal year 1978 budget. We can give you data supporting our fiscal year 1977 budget.

Mr. FLOOD. Will all of the institutes have this program?

Mr. SCHWARTZ. Yes, sir, they will.

Mr. FLOOD. Submit for the record a report of the activities and methodology that NIH is utilizing to assess its manpower needs and what institutes are participating. The staff would also be interested in any data you have to support your current request.

Mr. SCHWARTZ. Yes, sir.

[The information follows]:

MANPOWER MANAGEMENT PROGRAM AT NIH

The DHEW manpower management program was implemented at NIH in fiscal year 1972. The goal of MMP was to survey all agency positions over a four-year period, and, where appropriate, to establish workload and manpower measures. Over the years, it has gone through an evolutionary process of refinement.

The focus of MMP in the first 2 years of operation was on individual work measurement studies and manpower surveys in segments of NIH. By fiscal year 1975, NIH had conducted 15 manpower surveys and 5 work measurement studies covering approximately 40 percent of all positions, excluding intramural positions (intramural research is not considered subject to output measurement). Two important studies were conducted in the National Cancer Institute and the clinical center. As a result of these studies, the NCI developed a manpower and workload forecasting system covering 700 positions and the CC implemented the resource monitoring system covering 1,500 positions.

Beginning in 1974, NIH initiated another aspect of the MMP by conducting zero base analyses to justify position requests in preliminary budgets. The first ZBA's were developed by NCI and the CC for the fiscal year 1975 and fiscal year 1976 budget requests. For fiscal year 1977, all NIH components seeking position increases were included in the ZBA. Furthermore, the fiscal year 1978 ZBA will

cover all NIH components whether or not hey are requesting position increases. Consequently, all NIH components will be performing manpower and workload analyses for the fiscal year 1978 budget development and will provide fiscal year 1976, fiscal year 1977 and fiscal year 1978 workload and manpower data.

The latest refinement in the MMP began in fiscal year 1975 with the decision to develop an NIH workload/manpower reporting system. The target date for completion is July 1976. The W/MRS is based on a set of standardized agency activities and subactivities. Some of these activities are unique to one organizational component, such as printing services, small animal services and nursing services, while others cut across organizational lines, such as personnel management, financial management and program direction. Each activity will have one or more associated output measures.

Where an activity includes multiple outputs that vary in substance, we will attempt to generate a "principal output" to represent the total activity.

Where outputs vary in size and complexity (for example, the various types of research grants), we will establish weights to account for the differences.

Where outputs are not subject to measurement (for example, the output of an institute's direct research), requested staffing will continue to be based on level-of-effort and programmatic justifications.

The W/MRS will provide NIH, through quarterly reports, current and standardized manpower data on both an organizational and functional basis for use in manpower forecasting and budget justification.

PEER REVIEW SYSTEM

Mr. FLOOD. Has NIH completed the study of the peer review system? If you have, what was your finding?

Dr. FREDRICKSON. We have not yet completed it. We are about to hold the third of three public hearings that we are conducting.

RESEARCH TRAINING

Mr. FLOOD. There is no legislation currently on the books for research training. However, I am sure we are going to have that legislation very shortly. Why does the budget call for a phaseout of institutional training grants? That type of training grant was authorized by the original law. You are phasing it out. Why?

Dr. FREDRICKSON. We actually have two kinds of training grants, Mr. Chairman. The ones authorized under the original law are being phased out because their authorization no longer obtains. We are phasing out only those that were funded prior to the enactment of the new legislation.

Mr. FLOOD. That being so, what impact will this phaseout of training grants have upon the universities?

Dr. FREDRICKSON. Some of these training positions will be replaced by the National Research Training Act awards but the the total effect will be a decrease in the training grants to the universities.

Mr. FLOOD. In this budget you propose to emphasize the postdoctoral rather than predoctoral.

Dr. FREDRICKSON. That is correct, sir.

Mr. FLOOD. What effect is that going to have on future manpower?

Dr. FREDRICKSON. It will tend to decrease the number of people in the national research program who are trained at Federal expense.

Mr. FLOOD. I am talking about the other study. What is the status of that study required by the original research legislation to determine the overall need and the kind of manpower?

Dr. FREDRICKSON. That is being conducted by the National Academy of Sciences and their report is expected shortly.

Mr. FLOOD. Then it isn't completed.

Dr. FREDRICKSON. No.

Mr. FLOOD. If it isn't completed, how in the world do you decide which training to emphasize in fiscal 1977? How did you do that, with mirrors?

Dr. FREDRICKSON. Partly, but we will of course be very attentive to the recommendations in that report in issuing our awards.

Mr. FLOOD. That is encouraging.

DIABETES RESEARCH PLAN

The National Commission on Diabetes specifically identifies the Director, NIH, as the person responsible for implementing the diabetes research and training center program. How do you plan to carry out that responsibility? Do you have a formal plan?

Dr. FREDRICKSON. Yes.

Mr. FLOOD. If you have a formal plan, then let's put that in the record.

Dr. FREDRICKSON. The plan is as follows——

Mr. FLOOD. Do you have a formal plan?

Dr. FREDRICKSON. Not yet a written plan ready for publication but that is being developed.

Mr. FLOOD. When are you going to have it?

Dr. FREDRICKSON. I expect to have the recommendation of the interagency——

Mr. FLOOD. When are you going to have the formal plan?

Dr. FREDRICKSON. I should have the guidelines in 2 weeks and the formal plan as soon as possible after that.

Mr. FLOOD. If that happens before this record is printed will you see that it is in the record?

Dr. FREDRICKSON. Yes.

FUNDS FOR NATIONAL EYE INSTITUTE

Mr. FLOOD. Doctor, you have told us that you had a much freer hand in developing this NIH budget. You have touched on that several times. That being the case, can you explain how you decided to reduce the Eye Institute budget by $3,325,000 while you increased the National Library of Medicine by $6 million. You are the people who told us that all kinds of visual problems cost the economy over $5.2 billion a year.

Dr. FREDRICKSON. The reason the Eye Institute shows a negative increment between——

Mr. FLOOD. It shows all right. I am surprised by this gobbledygook. Downtown we expect that but not from your campus. You are getting poisoned. You better have another institute out there.

All right. You cut it $3,335,000—exclamation point.

Mr. PATTEN. That is a negative increment.

Dr. FREDRICKSON. The difference between the 1977 budget before you and the final 1976 appropriation does show a reduction of $3.3 million.

Mr. FLOOD. Now you have stated the question. What is the answer?

Dr. FREDRICKSON. The answer is, sir, that at the time we made this allocation we were working on a different base.

Mr. FLOOD. Different base?

Dr. FREDRICKSON. Yes, sir, we were using the continuing resolution.

Mr. FLOOD. What does that have to do with cutting the eye people over $3 million and giving the National Library of Medicine plus $6 million?

Dr. FREDRICKSON. We actually thought we were increasing the eye appropriation by $2.6 million, with the base that we were operating upon, sir.

Mr. FLOOD. I tell you what you do. When you get time, talk that over with your brothers and submit something for us on the record.

That will take quite an answer.

[The information follows:]

GENESIS OF THE NEGATIVE INCREMENT IN THE FISCAL YEAR 1976 BUDGET ESTIMATE FOR THE NATIONAL EYE INSTITUTE

The fiscal year 1977 budget estimate for the National Eye Institute is $46,950,000. This compares with $44,110,000 available for obligation in fiscal year 1975 and an allowance of $44.301,000 under the continuing resolution for fiscal year 1976. The fiscal year 1977 budget estimate thus represented an increase of $2,649,000 over the expected 1976 obligational authority under the continuing resolution which was the operative legislation at the time the budget was submitted to the Congress.

However, passage of the fiscal year 1976 Labor-HEW appropriations bill (H.R. 8069) over the President's veto and the President's subsequent decision not to request a rescission raised the amount available for obligation by the National Eye Institute in fiscal year 1976 to $50,285,000. The amount requested in the fiscal year 1977 budget is therefore $3,335,000 less than the amount actually appropriated for fiscal year 1976.

The difference in the fiscal year 1976 base on which the bulget estimate was calculated and the higher amount now actually available for fiscal year 1976 has converted what was intended to be a $2.6 million increase into a $3.3 million decrease.

As the total amount requested for fiscal year 1977 ($46,950,000) remains constant, there is no change in the level of activity which that amount was intended to support. However, as the level of activity in fiscal year 1976 will now be greater than had been expected when the fiscal year 1977 budget was formulated—due to the congressional increase of $5,984,000 in the appropriation, as compared with the allowance under the continuing resolution—the fiscal year 1977 budget request will require a reduction of a little over half of the fiscsal year 1976 increase in program activity.

Mr. FLOOD. Mr. Michel?

GRANTS AND CONTRACTS

Mr. MICHEL. Thank you, Mr. Chairman.

Doctor, I am not going to be dealing so much on specific figures here this afternoon but rather confine my questions pretty much to the one area having to do with grants and contracts because that is a significant amount of your appropriation.

Last year the chairman asked Dr. Lamont-Havers to submit for the record a list of the numbers of grants and contracts by each Institute. I would like to have you do it again for this year even if the figures for fiscal year 1976 are estimates due to the lateness of the appropriation bill.

Dr. FREDRICKSON. Yes, sir.

[The information follows:]

DHEW-NIH ESTIMATED NUMBER OF GRANTS AND CONTRACTS

	Fiscal year 1976		Fiscal year 1977	
	Research	Regular research grants	Research	Regular research grants
Cancer	969	2,181	796	1,660
Heart	350	1,954	300	1,619
Dental	63	341	70	377
Arthritis	94	1,949	110	1,810
Neurology	66	1,228	69	1,203
Allergy	132	1,100	145	1,111
General Medical Sciences	11	1,919	11	1,754
Child Health	196	1,175	192	1,046
Aging	18	95	23	158
Eye	25	575	30	528
Environmental	21	168	27	206
Research Resources	21	----------	18	----------
National Library of Medicine	90	----------	105	----------
Total	2,056	12,685	1,896	11,472

Mr. MICHEL. In fiscal 1975 there were, I believe, nearly 16,000 grants and contracts awarded by NIH. What would be your estimate of the figure for fiscal 1976?

Dr. FREDRICKSON. For 1976 the total research grants will be 12,685.

Mr. MICHEL. Do you have a projection for 1977?

Dr. FREDRICKSON. 11,472.

Mr. MICHEL. How many of these are likely to be new grants both in 1976 and 1977?

Dr. FREDRICKSON. In 1976 the new grants would be 1,753.

Mr. MICHEL. 1977?

Dr. FREDRICKSON. 827.

Mr. MICHEL. Last year we were told the average length of a grant is 3.2 years. Am I correct in assuming this does not count the instance where the researcher, at the end of his grant, applies for a renewal of his grant?

Dr. FREDRICKSON. Those would be competing renewals.

Mr. MICHEL. A competing renewal?

Dr. FREDRICKSON. Yes. I have not given you the figure for those grants.

Mr. MICHEL. How many of those would there be?

Dr. FREDRICKSON. In 1976 there will be 1,812 and in 1977 it is estimated 1,154.

Mr. MICHEL. Now what do we have outstanding, roughly 13,000, then? Grants outstanding. Would that be in the neighborhood of 13,000 or would we take this 12,685 figure, or is it more than that?

Dr. FREDRICKSON. The figure is 12,685.

Mr. MICHEL. What percentage of grant recipients apply for renewal once their initial grant period is up?

Dr. FREDRICKSON. Seventy to eighty percent.

Mr. MICHEL. What percentage normally receive approval out of those?

Dr. FREDRICKSON. This varies considerably among the several Institutes. We can give you, for example, figures for any given Institute.

Mr. MICHEL. Why don't you take the Institutes and give me that rate of approval for each one; would you? You can give me that for the record.

[The information follows:]

Approval rates for competing renewal research grants by NIH component, fiscal year 1975

NIH component:	Percent approved
NCI	85.6
NHLI	87.8
NIDR	76.7
NIAMDD	93.2
NINCDS	93.5
NIAID	97.6
NIGMS	95.8
NICHD	87.5
NIA	100.0
NEI	93.7
NIEHS	91.7
DRR	87.8
NLM	73.4
Total, NIH	90.8

RESEARCH ACCOMPLISHMENTS

Mr. MICHEL. After a grant expires, is the researcher required to submit a report of his findings to NIH?

Dr. FREDRICKSON. Yes; he is.

Mr. MICHEL. In what percentage of the grants would you say that the results were generally inconclusive, that there is very little in the way of scientific accomplishment or advancement?

Dr. FREDRICKSON. I can only guess, Mr. Michel. I don't know. My guess would be it is a relatively small fraction in which there was no addition to scientific knowledge.

Mr. MICHEL. Do you make any special study to determine that?

Dr. FREDRICKSON. Actually, the difficulty with that study is that one often cannot determine, even for years, whether or not those results have been significant. Sometimes they have cropped up again years later as the basis for some significant extrapolation, in connection with other new data, after years of being relatively useless by themselves. A piece of a jig-saw puzzle is not important until you have a place to put it.

DUPLICATION OF RESEARCH

Mr. MICHEL. With 12,000 to 13,000 grants being awarded, there has to be some overlapping and duplication. Are you concerned about that?

Dr. FREDRICKSON. Possibly there is some duplication but in my own opinion, Mr. Michel, it is not a very serious problem.

Mr. MICHEL. How do you guard against it?

Dr. FREDRICKSON. By the various studies that set the scientific priorities. Scientists are very loath to reproduce what someone else has done. Study sections are merciless in weeding out simple repetition of research already done. One of our problems is that we don't have enough repetition in some instances. For example, if one scientist has worked out the amino acid chain of a great, long important protein, it is very difficult to get some other scientist to do it because little reward is attached to the second runthrough to check; but yet this can be extremely important.

SIZE OF GRANTS

Mr. MICHEL. What is the dollar amount of these grants on an average?

Dr. FREDRICKSON. Between $60,000 and $70,000.

Mr. MICHEL. Do you have any grants over $1 million?

Dr. FREDRICKSON. They would only be a very few large center grants.

Mr. MICHEL. Those that are over $1 million, list in the record, would you?

Dr. FREDRICKSON. Yes, sir.

[The information follows:]

NIH GRANTS AWARDED FOR $1,000,000 OR MORE, FY 1975

GRANT NUMBER	INSTITUTION PROJECT TITLE	PRINCIPAL INVESTIGATOR	TOTAL AWARDED
1 C06 CA15023-01	YESHIVA UNIVERSITY NEW CANCER FACILITY	FRIEDMAN, EPHRAIM	8,649,562
1 C06 CA16604-01	COLUMBIA UNIVERSITY NEW CANCER FACILITY	PUTNEY, FREDERICK B	5,890,095
1 C06 CA16595-01	UNIVERSITY OF CALIFORNIA LOS ANGELES EXISTING CANCER FACILITY	STECKEL, RICHARD J	5,062,500
1 C06 CA17420-01	SIDNEY FARBER CANCER CENTER CANCER FACILITY	FREI, EMIL, III	4,896,863
1 C06 CA13706-01	SALK INSTITUTE FOR BIOLOGICAL STUDIES LABORATORY ANIMAL RESEARCH FACILITY	BERNSTEIN, JAMES E	1,800,000
3 C06 CA16360-01A151	YALE UNIVERSITY REMODELING NEW CANCER FACILITY	BERTINO, JOSEPH	1,274,372
2 M01 RR00036-15	WASHINGTON UNIVERSITY SUPPORT FOR GENERAL CLINICAL RESEARCH CENTER	KIPNIS, DAVID M	1,415,241
1 M01 RR00888-01	PETER BENT BRIGHAM HOSPITAL GENERAL CLINICAL RESEARCH CENTER	BRAUNWALD, EUGENE	1,237,100
5 M01 RR00079-13	UNIVERSITY OF CALIFORNIA SAN FRANCISCO SUPPORT FOR GENERAL CLINICAL RESEARCH CENTER	FORSHAM, PETER H	1,161,015
2 M01 RR00047-15	CORNELL UNIVERSITY MEDICAL CENTER SUPPORT FOR GENERAL CLINICAL RESEARCH CENTER	BUCHANAN, J ROBERT	1,005,060
5 P30 CA08748-10	SLOAN KETTERING INSTITUTE FOR CANCER RES CANCER RESEARCH PROGRAM	GOOD, ROBERT A	8,745,614
5 P01 CA05826-14	MEMORIAL HOSPITAL FOR CANCER-ALLIED DIS CLINICAL CANCER RESEARCH CENTER	BURCHENAL, JOSEPH H	4,502,562
2 P01 HL06285-15	UNIVERSITY OF CALIFORNIA SAN FRANCISCO CARDIOVASCULAR - RESPIRATORY PHYSIOLOGY AND BIOCHEMISTRY	HAVEL, RICHARD J	3,783,643
1 P60 HL17269-01	BAYLOR COLLEGE OF MEDICINE DEMONSTRATION CENTER FOR HEART AND VESSEL DISEASE	DE BAKEY, MICHAEL E	3,005,678

SOURCE: IMPAC FILE/DRU,SAB,DRG IRS PROGRAM-F599

NIH GRANTS AWARDED FOR $1,000,000 OR MORE, FY 1975

GRANT NUMBER	INSTITUTION PROJECT TITLE	PRINCIPAL INVESTIGATOR	TOTAL AWARDED
5 P01 CA06927-13	INSTITUTE FOR CANCER RESEARCH BIOLOGICAL AND BIOCHEMICAL PROGRAM IN CANCER RESEARCH	TALBOT, TIMOTHY R, JR	2,744,892
5 P01 CA07175-12	UNIVERSITY OF WISCONSIN MADISON CANCER RESEARCH AT THE MC AROLE LABORATORY	PITOT, HENRY C	2,735,950
5 P40 RR00163-16	MEDICAL RESEARCH FOUNDATION OF OREGON SUPPORT FOR REGIONAL PRIMATE RESEARCH CENTER	HOLMAN, CHARLES N	2,404,829
5 P30 CA14089-02	UNIVERSITY OF SOUTHERN CALIFORNIA PILOT MULTIDISCIPLINARY CANCER RESEARCH PROGRAM	HAMMOND, G DENMAN	2,346,554
5 P01 HL09011-12	COMMUNITY BLOOD COUN GREATER N Y RESEARCH AND RESOURCE BLOOD PROGRAM	KELLNER, AARON	2,261,262
5 P30 CA14599-02	UNIVERSITY OF CHICAGO CANCER RESEARCH PROGRAM	ULTMANN, JOHN E	2,151,628
5 P01 HL11310-09	UNIVERSITY OF ALABAMA IN BIRMINGHAM MECHANISMS OF CARDIOVASCULAR DISEASE	JAMES, THOMAS N	2,137,654
5 P01 CA10815-07	WISTAR INSTITUTE OF ANATOMY AND BIOLOGY CONSOLIDATED BASIC CANCER RESEARCH PROGRAM	KOPROWSKI, HILARY	2,129,810
5 P50 HL14236-05	ROCKEFELLER UNIVERSITY RESEARCH IN PREVENTION OF PREMATURE ARTERIOSCLEROSIS	AHRENS, EDWARD H, JR	2,091,369
5 P30 CA14520-03	UNIVERSITY OF WISCONSIN MADISON SUPPORT FOR CANCER RESEARCH CENTER	RUSCH, HAROLD P	2,031,865
5 P01 CA05838-14	STANFORD UNIVERSITY CANCER CENTER SUPPORT GRANT (SPECIALIZED)	KAPLAN, HENRY S	1,918,961
5 P01 CA14395-03	UNIVERSITY OF MIAMI COMPREHENSIVE CANCER CENTER OF GREATER MIAMI	ZUBROD, CHARLES G	1,775,542
2 P30 CA13148-04	UNIVERSITY OF ALABAMA IN BIRMINGHAM CANCER CENTER SUPPORT GRANT (COMPREHENSIVE)	DURANT, JOHN R	1,757,265
5 P01 CA13053-04	WASHINGTON UNIVERSITY CLINICAL CANCER RADIATION ONCOLOGY CANCER CENTER	POWERS, WILLIAM E	1,710,239

SOURCE: IMPAC FILE/DRU,SAB,DRG IRS PROGRAM-F599

NIH GRANTS AWARDED FOR $1,000,000 OR MORE, FY 1975

GRANT NUMBER	INSTITUTION PROJECT TITLE	PRINCIPAL INVESTIGATOR	TOTAL AWARDED
5 P01 CA13106-04	COLD SPRING HARBOR LABORATORY CANCER RESEARCH PROGRAM	WATSON, JAMES D	1,668,215
5 P40 RR00167-15	UNIVERSITY OF WISCONSIN MADISON SUPPORT FOR REGIONAL PRIMATE RESEARCH CENTER	BOCK, ROBERT M	1,646,243
2 P50 GM17702-06	UNIVERSITY OF CALIFORNIA SAN DIEGO STUDY OF HUMAN BIOCHEMICAL GENETICS	SEEGMILLER, JARVIS E	1,579,271
5 P30 CA15704-02	FRED HUTCHINSON CANCER RESEARCH CENTER CANCER CENTER SUPPORT GRANT (COMPREHENSIVE)	HUTCHINSON, WILLIAM B	1,575,521
5 P50 DE02731-09	UNIVERSITY OF MICHIGAN SUPPORT FOR DEVELOPMENT OF DENTAL RESEARCH INSTITUTE	MANN, WILLIAM R	1,575,000
5 P40 RR00166-15	UNIVERSITY OF WASHINGTON REGIONAL PRIMATE RESEARCH CENTER	GRAYSTON, J THOMAS	1,563,892
5 P01 CA13330-04	YESHIVA UNIVERSITY CANCER RESEARCH PROGRAM	EAGLE, HARRY	1,543,390
5 P50 GM15431-09	VANDERBILT UNIVERSITY RESEARCH CENTER FOR PHARMACOLOGY AND DRUG TOXICOLOGY	OATES, JOHN A	1,542,119
5 P01 CA08480-10	ST. JUDE CHILDREN'S RESEARCH HOSPITAL CHILDHOOD CANCER RESEARCH CENTER	MAUER, ALVIN M	1,471,637
5 P01 CA15936-02	MOUNT SINAI SCHOOL OF MEDICINE SPECIALIZED CANCER CENTER	HOLLAND, JAMES F	1,461,261
5 P41 RR00003-14	UNIVERSITY OF CALIFORNIA LOS ANGELES MEDICAL DATA PROCESSING RESEARCH	DIXON, WILFRID J	1,452,285
2 P40 RR00169-14	UNIVERSITY OF CALIFORNIA DAVIS SUPPORT FOR REGIONAL PRIMATE RESEARCH CENTER	PRITCHARD, WILLIAM R	1,452,228
5 P01 AI07007-10	SCRIPPS CLINIC AND RESEARCH FOUNDATION IMMUNOPATHOLOGIC STUDIES	DIXON, FRANK J	1,447,351
5 P40 RR00164-14	TULANE UNIV DELTA REG PRIMATE RES CTR SUPPORT FOR REGIONAL PRIMATE RESEARCH CENTER	WALSH, JOHN J	1,441,473

SOURCE: IMPAC FILE/DRU,SAB,DRG IRS PROGRAM-F599

NIH GRANTS AWARDED FOR $1,000,000 OR MORE, FY 1975

GRANT NUMBER	INSTITUTION PROJECT TITLE	PRINCIPAL INVESTIGATOR	TOTAL AWARDED
5 P50 DE02668-09	UNIVERSITY OF NORTH CAROLINA CHAPEL HILL REGIONAL DENTAL RESEARCH CENTER	HIRSCH, PHILIP F	1,400,000
2 P50 DE02600-09	UNIVERSITY OF WASHINGTON A RESEARCH CENTER IN ORAL BIOLOGY	SREEBNY, LEO M	1,397,000
5 P01 CA02332-21	COLUMBIA UNIVERSITY CLINICAL & LABORATORY NORMAL & ABNORMAL GROWTH STUDIES	SPIEGELMAN, SOL	1,354,676
5 P50 DE02670-09	UNIVERSITY OF ALABAMA IN BIRMINGHAM INSTITUTE OF DENTAL RESEARCH	FULLMER, HAROLD M	1,353,524
5 P40 RR00165-15	EMORY UNIVERSITY SUPPORT FOR YERKES REGIONAL PRIMATE RESEARCH CENTER	MYERS, ORIE E, JR	1,344,991
1 P41 RR00961-01	UNIVERSITY OF CALIFORNIA BERKELEY FACILITY FOR AUTOMATED EXPERIMENTS IN CELL BIOLOGY	GLASER, DONALD A	1,326,000
5 P30 CA14236-02	DUKE UNIVERSITY COMPREHENSIVE CANCER CENTER SUPPORT GRANT	SHINGLETON, WILLIAM W	1,323,095
5 P50 DE02623-09	UNIVERSITY OF PENNSYLVANIA CENTER FOR ORAL HEALTH RESEARCH	MYERS, HOWARD M	1,310,000
5 P40 RR00168-14	HARVARD UNIVERSITY NEW ENGLAND REGIONAL PRIMATE RESEARCH CENTER	EBERT, ROBERT H	1,292,344
2 P30 CA11198-07	UNIVERSITY OF ROCHESTER SUPPORT FOR CANCER RESEARCH CENTER	COOPER, ROBERT A, JR	1,290,806
2 P30 ES00200-13	NEW YORK UNIVERSITY RESEARCH IN THE ENVIRONMENTAL HEALTH SCIENCES	NELSON, NORTON	1,288,493
1 P60 HL17292-01	UNIVERSITY OF VERMONT & ST AGRIC COLLEGE VERMONT LUNG CENTER	GREEN, GARETH M	1,275,236
5 P01 CA10893-07	BAYLOR COLLEGE OF MEDICINE CANCER RESEARCH PROGRAM	BUSCH, HARRIS	1,261,306
5 P41 RR00396-08	WASHINGTON UNIVERSITY A RESOURCE FOR BIOMEDICAL COMPUTING	COX, JEROME R, JR	1,259,100

SOURCE: IMPAC FILE/DRU,SAB,DRG IRS PROGRAM-F599
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NIH GRANTS AWARDED FOR $1,000,000 OR MORE, FY 1975

GRANT NUMBER	INSTITUTION PROJECT TITLE	PRINCIPAL INVESTIGATOR	TOTAL AWARDED
P30 CA06973-13	JOHNS HOPKINS UNIVERSITY SUPPORT FOR CLINICAL CANCER CENTER	OWENS, ALBERT H, JR	1,236,412
3 P01 CA13696-03	COLUMBIA UNIVERSITY SUPPORT FOR CLINICAL CANCER RESEARCH CENTER	MARKS, PAUL A	1,225,690
5 P01 CA06294-14	UNIVERSITY OF TEXAS SYSTEM CANCER CENTER SUPPORT FOR RADIOTHERAPY RESEARCH CENTER	FLETCHER, GILBERT H	1,208,632
2 P01 CA12542-04	UNIVERSITY OF TEXAS SYSTEM CANCER CENTER FAST NEUTRON THERAPY WITH TAMVEC CYCLOTRON	FLETCHER, GILBERT H	1,197,551
1 P50 HL17646-01	WASHINGTON UNIVERSITY STUDY OF ISCHEMIC HEART DISEASE	SOBEL, BURTON E	1,180,892
1 P50 HL17648-01	UNIVERSITY OF CHICAGO STUDY OF ISCHEMIC HEART DISEASE	RESNEKOV, LEON	1,169,347
1 P01 CA17404-01	SLOAN KETTERING INSTITUTE FOR CANCER RES IMMUNOBIOLOGY IMMUNODEFICIENCY AND CANCER	CHOI, YONG S	1,144,495
7 P50 HL18323-01	CORNELL UNIVERSITY MEDICAL CENTER HYPERTENSION CENTER	LARAGH, JOHN H	1,139,819
5 P01 CA16127-02	UNIVERSITY OF NEW MEXICO CANCER RESEARCH AND TREATMENT CENTER PROGRAM	KLIGERMAN, MORTON M	1,125,536
5 P50 HL14217-05	TEMPLE UNIVERSITY SPECIALIZED CENTER FOR THROMBOSIS RESEARCH	SHERRY, SOL	1,109,794
5 P01 HL13517-05	UNIVERSITY OF WASHINGTON STUDY OF CIRCULATORY PERFORMANCE AND PREDICTION	DODGE, HAROLD T	1,109,689
1 P01 CA17613-01	AMERICAN HEALTH FOUNDATION CORE SUPPORT, CANCER CENTER PROGRAM	WYNDER, ERNST L	1,106,349
5 P01 HL15265-02	UNIVERSITY OF MINNESOTA PROGRAM ON SURGICAL CONTROL OF THE HYPERLIPIDEMIAS	BUCHWALD, HENRY	1,104,862
5 P50 GM15253-09	UNIVERSITY OF WASHINGTON STUDY OF INHERITED DISEASES	MOTULSKY, ARNO G	1,088,219

SOURCE: IMPAC FILE/DRU,SAB,DRG IRS PROGRAM-F599
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NIH GRANTS AWARDED FOR $1,000,000 OR MORE, FY 1975

GRANT NUMBER	INSTITUTION PROJECT TITLE	PRINCIPAL INVESTIGATOR	TOTAL AWARDED
5 P01 CA10895-07	UNIVERSITY OF WASHINGTON ADULT LEUKEMIA RESEARCH CENTER	THOMAS, E DONNALL	1,076,851
2 P30 CA06551-12	INSTITUTE FOR CANCER RESEARCH SUPPORT FOR CLINICAL CANCER RESEARCH CENTER	TALBOT, TIMOTHY R, JR	1,062,491
2 P01 CA13038-04	ROSWELL PARK MEMORIAL INSTITUTE EXPERIMENTAL THERAPEUTICS AND CANCER DRUG PROGRAM	MIHICH, ENRICO	1,041,886
5 P01 HL06314-15	UNIVERSITY OF MINNESOTA IMMUNOLOGIC MECHANISMS IN CARDIOVASCULAR DISEASE	VERNIER, ROBERT L	1,036,046
5 P50 HL14201-05	UNIVERSITY OF CALIFORNIA SAN FRANCISCO SUPPORT FOR PULMONARY DISEASE RESEARCH CENTER	COMROE, JULIUS H, JR	1,030,237
1 P30 CA16672-01	UNIVERSITY OF TEXAS SYSTEM CANCER CENTER CORE SUPPORT GRANT--COMPREHENSIVE	HICKEY, ROBERT C	1,028,771
5 P01 HL08805-11	UNIVERSITY OF PENNSYLVANIA STUDY OF CARDIOVASCULAR AND PULMONARY PERFORMANCE	FISHMAN, ALFRED P	1,019,032
5 P50 AM17328-02	UNIVERSITY OF CALIFORNIA LOS ANGELES PEPTIC ULCER CENTER	GROSSMAN, MORTON I	1,015,311

MAJOR GRANT RECIPIENTS

Mr. MICHEL. Also, would you list for us the highest 20 or so recipient institutions and the amount and number of grants they receive.

Dr. FREDRICKSON. Yes, sir.

[The information follows:]

NIH RESEARCH GRANT SUPPORT—TOP RECIPIENT INSTITUTIONS

	Number of grants	Amount (thousands)
University of California, San Francisco	279	$27,457
Harvard University	300	26,163
Johns Hopkins University	299	26,009
University of Pennsylvania	242	25,568
University of Washington	237	25,509
University of Wisconsin, Madison	265	24,437
University of California, Los Angeles	277	23,943
Yale University	246	22,302
Stanford University	209	21,424
Columbia University	230	21,350
Washington University (St. Louis)	208	21,178
Yeshiva University	166	19,356
University of Chicago	180	19,198
University of Minnesota	258	18,660
Duke University	203	16,859
University of California, San Diego	182	16,153
University of Michigan	200	16,077
New York University	183	15,066
Cornell University	180	14,789
Sloan Kettering Institute	46	14,654
Total	4,390	416,150

COMPETING AND NONCOMPETING GRANTS

Mr. MICHEL. Would you distinguish for us the difference between noncompeting and competing grants.

Dr. FREDRICKSON In definition you mean?

Mr. MICHEL. Yes.

Dr. FREDRICKSON. A noncompeting grant is one which was awarded in a prior year but whose expiration date has not yet come. That is, a 3-year grant will be noncompeting for the next 2 successive years. During that time we must carry the amount to be awarded in the base because we have agreed to fund that grant for that period. That is the noncompeting base.

The competing renewals are those who competed successfully before and are now at the end of their committed grant period and are coming back into the cycle again, taking their same chances in competition with entirely new proposals.

Mr. MICHEL. So it is quite possible for the same grantee to be competing every 3 years in a sense?

Dr. FREDRICKSON. Yes, it is.

SIZE OF GRANTS

Mr. MICHEL. How do you determine the size of each grant?

Dr. FREDRICKSON. That determination is made by both the study section and the advisory council. The study section determination is perhaps the most important because there the experts know what is required to do the job that has been given a certain scientific priority.

The budgets actually are examined very carefully by experts, and in most instances some pruning occurs, sometimes very significantly so, but we decide what it costs to do the job that we agree appears to be possible and that we think should be done.

Mr. MICHEL. The grantee when he submits his application, of course, has a dollar figure.

Dr. FREDRICKSON. Yes.

Mr. MICHEL. Does that get amended very frequently?

Dr. FREDRICKSON. Very frequently.

Mr. MICHEL. Downward or upward?

Dr. FREDRICKSON. It is usually downward.

Mr. MICHEL. Is it ever upward?

Dr. FREDRICKSON. It may be. If a good idea is present in the grant, application and it is decided this would be important to support, the people judging it may know that it cannot be done with a particular piece of apparatus and they may recommend an increase in the budget for a different or more sophisticated piece of equipment.

INDIRECT COSTS

Mr. MICHEL. Moving to the question of overhead, does overhead include the salaries of researchers or is that a separate item?

Dr. FREDRICKSON. That is usually a separate item. It is a direct item as part of the project's budget when it is included in the grant application.

Mr. MICHEL. I understand overhead in many instances includes salaries of presidents, vice presidents, legal counsels, deans, department heads, administrative staffs, secretarial pools, librarians, grounds care people, and so forth. Is that true?

Mr. SCHWARTZ. Mr. Michel, there is a fairly detailed proscription on what elements of cost can be included in an overhead calculation. This is reviewed by a group of accountants located in the HEW regional offices. They are experienced in cost accounting principles and follow a well known set of principles that are used as a basis for developing the overhead rate. There are differences of opinion between institutions as to what should be included in this rate. From the result of the negotiations we get an approved rate that is then used for all grants and contracts that go to that institution.

Some of the items that you used as examples of elements of cost included in overhead are correct. They are considered to be an appropriate cost of overhead for conducting research.

Mr. MICHEL. Is there a rule of thumb? What do you have, an instruction booklet or something the institution would tie to in this regard?

Mr. SCHWARTZ. Yes, sir, there is a Federal management regulation put out by the GSA.

Mr. MICHEL. Is it a lengthy thing?

Mr. SCHWARTZ. No, sir, it is not, and it does have a number, Federal management circular 73-8.

Mr. MICHEL. Is it a couple pages or more? I don't want to clutter up the record.

Mr. MILLER. You may want even more than that, Mr. Michel. It is fairly lengthy but perhaps not too lengthy for the record, but the

Department has proposed a revision of that circular and the comments are being collected by GSA now. It is very controversial, and the very items you just read off your list are among the items of very hot controversy now with the schools. You may wish to see both the existing circular and the proposed changes, but those changes are by no means anywhere near final. All the comments are not in yet.

Mr. MICHEL. Why don't we have the staff determine whether it is too big for the record. If it is reasonable let's have it in the record.

[Clerk's note: Because of its length, this information does not appear. It is available in committee files.]

Mr. MICHEL. Did you say there are some suggested changes?

Mr. MILLER. It is about as long as the original document itself. I have seen it, but I can't remember the length.

Mr. MICHEL. Let's have both and the staff can determine whether we can effectively place them in the record.

[Clerk's note: Because of its length, this material does not appear.]

Mr. MICHEL. Some institutions hire people to help their staff to get still more grants. Are the salaries of these people included in overhead?

Mr. SCHWARTZ. In many institutions there is a director of sponsored research, and that individual and his staff would be an allowable cost item.

Mr. MICHEL. I understand that some institutions receive overhead in excess of 60 percent of the total grant. That might be extreme but I have heard of such cases.

Mr. SCHWARTZ. Yes, sir, there are. This varies considerably. There are some institutions that put items into overhead that in other institutions would appear as a direct cost item, so you can't just look at the overhead rate to determine whether it is lower or higher than at another institution.

Mr. MICHEL. How do we get uniformity?

Mr. SCHWARTZ. That comes from the GSA regulation. It does specify what elements of cost can be included and what elements cannot. We do not, however, dictate to the institutions what they must include.

Mr. MICHEL. When you get into that area, I have to be very critical, and we had a rather spirited debate a number of years ago when we were talking about whether or not to just independently impose a flat percentage for overhead, 10, 15, 20, you name it.

You know, if my memory serves me correctly, overall I guess this overhead runs about 26 percent. Then when I look at $1.5 or $1.6 billion and I equate that with 26 percent, I say here is a chunk of subsidy to whatever institutions of higher learning. That is one of the reasons I am developing the line of questioning here because I am wondering if we have gone too far here without a little check as to where we are going.

Mr. MILLER. Mr. Michel, is it clear that a single rate is developed for a recipient institution for the whole Federal Government? For example, HEW generally has responsibilities for educational institutions, and our people in the regional offices will go in on the basis of the circular Mr. Schwartz and I have been describing and establish an indirect cost rate for grants for all Federal programs so that the same rate will be applied across the board.

Dr. FREDRICKSON. I think it would be well to say, Mr. Michel, that we recognize this problem but we do feel that where a cost can actually be attributed to the cots of doing research, when we seek to have that research done, we should bear as much of the reasonable share of that cost as we can, so it doesn't become an unreasonable burden on an institution to have accepted the research.

Mr. MICHEL. Then, you see, one institution reaches a ceiling, and then, well, if it is good enough for institution X we might as well get cut in on the same action so institution Y comes along and plays the same game, and after a while we are up there in the clouds again.

I think my figures of a 26-percent overall overhead are correct, are they not? That is made up from extremes running from what to what?

Mr. SCHWARTZ. We can provide that for the record, Mr. Michel, but I think you should not just look at the rate itself but examine the cost principles. If the cost principles are agreed upon in terms of what overhead items can be allocatable to research, then the cost accountants can develop what the appropriate rate would be.

I might just add that there are not very many industrial profitmaking organizations doing research who have overheads less than 100 percent. If you compare university overhead rates to those of profitmaking and also other nonprofit-institutions, I think you will find they will compare very favorably. Again I would not put the emphasis on the rate but rather on the cost principles.

Mr. MITCHEL. Would you say that the largest overhead, as a rule of thumb, would go to the larger institutions?

Mr. SCHWARTZ. No, sir. There is not a direct correlation.

Mr. MICHEL. If you had two similar grant applications but one came from an institution where the overhead was lower—they are obviously competing—would you tip the scales in favor of the one that had the lower overhead cost?

Mr. SCHWARTZ. When the grants are examined by the study sections, they only see the direct cost. We add the overhead cost at the end of the process because we might have a number of grants from one institution during a month, and rather than add the cost to the individal grants, we add it as a lump sum at the end of the month. When the study sections examine grant applications they do not have available to them the indirect cost rates.

Mr. MICHEL. Are we doing anything in NIH to admonish these institutions to try to keep their overhead down as tight as they possibly can?

Mr. SCHWARTZ. I think NIH is doing a very good job of reviewing audit reports by HEW auditors and dealing with the institutions in correcting poor management processes. That is our prime relationship with the institutions. The actual negotiations and review of overhead are done by the regional offices.

Mr. MICHEL. Is there uniformity among those regional offices?

Mr. SCHWARTZ. Yes; there is one office in the Department that is responsible for insuring that there is a common policy across the United States.

RESEARCH AND TEACHING

Mr. MICHEL. I have heard that in some institutions, promotion, tenure, and raises are often dependent on a faculty member getting

research grants, with the result being that first-class teachers who aren't particularly interested in research are pressured to seek research grants. Have you found any indication of this, and if so, what are you doing to discourage such practices?

Dr. FREDRICKSON. A study is being conducted by an outside contractor for us in this regard. The preliminary results suggest very little correlation between whether or not the individual has been awarded a grant and his opportunity for promotion. I have no doubt that it makes some difference, but I think the factors that really determine promotion are extremely hard to predict and not entirely related to that.

INDIRECT COSTS

Mr. MICHEL. I have been told that some of the scientists themselves have objected to the high overhead involved, but that the administrators have told them that is no concern of theirs.

What is your reaction to that?

Dr. FREDRICKSON. Our principle would be to certainly not pay for more than the reasonable cost of doing research, but we are governed by the overall principle which we don't ourselves determine.

DISTRIBUTION OF GRANTS

Mr. MICHEL. Could you give me—just finally winding up, Mr. Chairman—what percentage of our grants and contracts are going to private research organizations, what to medical schools, and then what to just universities in general? Do you have a breakdown of that?

Dr. FREDRICKSON. We can supply that breakdown for the record.

Mr. MICHEL. Yes.

[The information follows:]

NIH grants and contracts awarded in fiscal year 1975 by type of organization

	Percent
Domestic nonprofit	100.0
Research institutes, laboratories, and foundations	10.6
Medical schools	55.0
Other institutions of higher education	23.1
All other domestic nonprofit	11.3

Mr. MICHEL. Of those grants going to private research organizations, what average percentage of each grant is paid out in salaries and what is the average percentage allocated for overhead in those institutions?

Dr. FREDRICKSON. We will supply that.

[The information follows:]

NIH research grants awarded to private research organizations

	Percent
Percentage used for personnel costs based on latest available direct cost expenditures	69.4
Average indirect cost rate to direct costs for research grants awarded during fiscal year 1975	36.7

SALARIES INCLUDED IN GRANTS

Mr. MICHEL. What are the average salaries for researchers in private research organizations, and what percentage are normally paid for by the Federal grant?

Dr. FREDRICKSON. We will supply that as best we can.

[The information follows:]

SALARIES FOR RESEARCHERS IN PRIVATE RESEARCH INSTITUTIONS

NIH does not capture salary information as it pertains to an idividual nor does NIH obtain salary scales from grantee institutions and organizations. Thus, the information requested is not available from NIH for insertion in the record. The NIH follows the policy as set by the Department of Health, Education, and Welfare for the reimbursement to grantee institutions for services rendered by their employees: Salaries for professional and nonprofessional personnel service in the conduct of NIH-supported research will be reimbursed on the basis of the total salary commitment in proportion to the time or effort devoted to any specific NIH supported project. The grantee institution determines what the total salary will be, on the basis of its usual policies.

The proportion of salaries paid to individuals from NIH research grants varies widely in proportion to the effort to be devoted to the research ranging from 5 or 10 percent to the full salary. A special report prepared from information obtained from non-NIH sources will be provided your staff. It represents the only tracking of academic salaries done by NIH staff.

Mr. MICHEL. According to testimony last year, the average salary of principal investigators at certain sample universities was $54,000. What is the average percentage of such salary paid for by Federal grant money?

Dr. FREDRICKSON. Again we will attempt to develop those data as best we can.

[The information follows:]

SALARIES FOR PRINCIPAL INVESTIGATORS IN PRIVATE RESEARCH INSTITUTIONS

As noted in response to the request for information on salaries and percent paid by Federal grants for principal investigators in private research institutions, the NIH does not capture data about the salaries paid to individuals. A special study would be required to respond to this request.

Mr. MICHEL. Then, for universities, the average percentage of each grant paid out in salaries. I would like to have that.

Dr. FREDRICKSON. All right, sir.

[The information follows:]

PERCENTAGE OF NIH RESEARCH GRANTS USED FOR PERSONNEL COSTS

Institutions of higher education (based on latest direct cost expenditures available)—average percentage, 62.3.

Mr. MICHEL. When did NIH begin allowing universities to charge part of the investigator's salary to the grant?

Dr. FREDRICKSON. Almost from the beginning. In the 1950's.

Mr. MICHEL. Was there ever a debate on that subject in-house if it wasn't here in the Congress?

Dr. LAMONT-HAVERS. Yes; there was, Mr. Michel. Basically, it came down to the fact that if the Federal Government was indeed supporting the cost of biomedical research, then the actual salary of the individual investigator or anybody else doing the research was a legitimate charge to the grant itself. But there was a great deal of debate about this, particularly in the late 1950's.

RESEARCH AND TEACHING IN MEDICAL SCHOOLS

Mr. MICHEL. To what extent does the increase in participation in medical school faculty in NIH activities take them away from the teaching of medical school students?

Dr. FREDRICKSON. It is a difficult question to answer except by a detailed time study.

Our concern is that their necessary duties with medical students take them away from research, because that is what we are attempting to buy and to achieve. There is a delicate balance involved. I think that the NIH does put a good deal of demand on many institutions in order to get the knowledge it needs.

Mr. MICHEL. Could you expand on that. It is one I get asked so frequently.

Dr. FREDRICKSON. There are many who feel—and I am one of them—that direct involvement in research is necessary to the maintenance of the highest quality in medical and advanced scientific education. As a generalization, I would say that the schools and departments that do the best research also provide the best training at the doctoral and postdoctoral level.

A Ph. D. degree in any of the sciences is, or certainly should be, a research degree; a graduate department without a vigorous research program is a poor place in which to train Ph. D. candidates. This is not true, to anything like the same extent, for medical students who must cover an immense amount of ground in a very short time and are expected to accept much of what they learn on faith. But this may well be one of the weaknesses in our system of medical education. To some extent it is an unavoidable weakness because medicine is not yet as exact a science as the so-called physical sciences. Too much of our medical knowledge is still based on empirical deductions and observation for which there really is no sound acceptable scientific base. We still speak of medicine as an art for good reason. But it therefore all the more important to expose prospective physicians to the research side of their profession.

As I mentioned in my opening statement, the new science of bacteriology revolutionized the practice of medicine at the beginning of this century. The discovery of antibiotics brought about another profound change some 30 years ago. We are on the verge of further revolution on at least two fronts: Through the gradual unraveling of the cumulative effects of environmental factors in the causation of disease and through a growing understanding of the genetic mechanisms which promises to have major impact on both the treatment and the prevention of disease and disabilities.

I think it is safe to predict that before this year's medical school graduates have finished their professional careers, the practice of medicine will have been radically altered as the result of research. If that is so, it is surely the job of the medical school not merely to teach them the best that the practice of medicine now has to offer but also to prepare them, as much as possible, for the changes that lie ahead. In other words, they should have more than just a nodding acquaintance with biomedical research.

In a good teaching hospital, clinical research and cilinical instruction are already virtually inseparable entities. They are complementary and it would be difficult to show, and foolhardy to allege, that one detracts from the other. Quite the contrary.

A more mundane but equally important reason for maintaining a vigorous research program in a medical school is that it is an important factor in attracting first-rate faculty. The qualities that make a good researcher—professional competence, curiosity, insight, imagination, persistence and drive—are the qualities which a conscientious student

most hopes to find in his preceptor. And, I suppose, one could view the existence of a large number of grant-supported research projects at a medical school as an endorsement or measure of the quality of its faculty, at least as seen by their scientific peers who serve on NIH study sections.

In short, Mr. Michel, I do not see any basic conflict betweeen research and teaching. Research is inextricably bound up in the teaching process. Teaching, research and clinical practice have gone hand in hand at American medical schools since the reforms brought about in our system of medical education in the wake of the famous Flexner report in 1910. It is essential that the base of medical education be scientific. There are also other demands too, such as, for caring, efficient delivery, and effective organization, but the schools have the burden of providing this without relinquishing their close touch with and involvement in research.

Mr. MICHEL. I may have a few more, Mr. Chairman.

Mr. FLOOD. Mr. Natcher.

Mr. NATCHER. Not at this point, Mr. Chairman.

Mr. MICHEL. Mr. Shriver.

"NEWS AND FEATURES FROM NIH"

Mr. SHRIVER. Dr. Frederickson, you devoted a substantial amount of your statement to your efforts to improve the dissemination of research results. One of your past efforts in this regard was a press release issued periodically entitled "News and Features from NIH." Do you still put that out?

Dr. FREDERICKSON. I think we do, Mr. Shriver.

Mr. SHRIVER. I ask because I used to get them.

Dr. FREDERICKSON. I think we may put them out in a different form. Are you now receiving them, Mr. Shriver?

Mr. SHRIVER. No. I recall one of the articles in the publication concerned using female dogs as substitute mothers for baby monkeys. After I mentioned that in last year's hearings, my subscription apparently ran out.

Dr. FREDRICKSON. We certainly will see that you do get it.

EXPENDITURE ON DISSEMINATION

Mr. SHRIVER. How much of your budget would you estimate goes for dissemination efforts either to the medical profession or to the public?

Dr. FREDRICKSON. I will supply a more detailed estimate for the record but it is relatively small, on the order of tens of thousands, not counting personnel costs. Less than a million.

Mr. SHRIVER. I assume that is a rather important part of your work. If you do have a figure, put it in the record.

Dr. FREDRICKSON. Yes, sir.

[The information follows:]

EXPENDITURE ON DISSEMINATION

The NIH Office of Communications which handles public information will spend $250,000 this year for television and radio material, publications, postage, and other costs other than personal services.

In January, a fund of $235,000 was established to support special projects for dissemination of research information to health professionals.

Mr. SHRIVER. You say you are presently operating at a spending level of the President's revised budget for 1976.

Dr. FREDRICKSON. We are now operating under the appropriation.

Mr. SHRIVER. I am talking about page 12.

Dr. FREDRICKSON. We are operating on the appropriation as passed over the President's veto.

ENVIRONMENTAL RESEARCH

Mr. SHRIVER. You observe that the field of environmental research may prove as fruitful as the discovery of bacteria as a cause of disease. Would you expand on that subject?

Dr. FREDRICKSON. Yes. I meant by that, Mr. Shriver, that it is very clear that an increasing number of compounds are being introduced into the environment largely through the process of industrialization, the search for new energy forms and other needs to maintain the economy. Here is an area which is largely unknown in terms of the possible effects of these materials, in various concentrations, on human disease and on the adaptation of the human being. It is also an extraordinarily difficult area. A whole new set of techniques has to be developed for attempting to assess the possible harmful effects of these substances. The cumbersome methods of giving different materials to animals is very expensive and very time consuming. There are some exciting new developments in using cells in tissue culture for much more rapid testing, at least in a preliminary form, for determining whether a given compound in a given amount might be harmful.

AMBULATORY CARE RESEARCH FACILITY

Mr. SHRIVER. If everything goes well, when do you expect the new ambulatory research facility to be functioning?

Dr. FREDRICKSON. If funds were received by October of this year, an ambitious, but I think probably realistic, estimate would be that we might be able to open the doors in December 1980.

NEW GRANTEES

Mr. SHRIVER. You made a good argument at the conclusion of your statement for a mix of old and new research projects. Will you tell us approximately what that mix is this year?

Dr. FREDRICKSON. In terms of the regular research grant—which is our standard instrument, the one we began with—approximately 10 percent of those awarded each year are to new people entering the system for the first time. The remainder then will have been there for varying periods of time. But it is that constant movement inward of new people that is very important in maintaining the life and the vigor of such a system.

MINORITY BIOMEDICAL RESEARCH SUPPORT

Mr. SHRIVER. The Senate report on our fiscal 1976 bill directed NIH under the minority biomedical research support grant to make available $100,000 to Haskell Indian Junior College in Lawrence, Kans. That is not in my district. Have those funds been awarded?

Dr. FREDRICKSON. I will have to find out, Mr. Shriver. We will certainly inform you of that.

[The information follows:]

MINORITY BIOMEDICAL SUPPORT

No funds have been awarded to the Haskell Indian Junior College. Haskell College is administered by the Bureau of Indian Affairs, which is part of the Department of Interior. We are awaiting legislative authorization allowing us to fund grants to Government agencies other than the Veterans' Administration. The authorization which is part of the heart and lung authorizing legislation bill is currently in conference (H.R. 7988). If this bill is passed the award will be made.

Mr. SHRIVER. Thank you, Mr. Chairman.

Mr. FLOOD. Mr. Patten.

NIH MORALE

Mr. PATTEN. Doctor, it is hard to believe that you think your staff has good morale and everything is sunshiny up your way.

Dr. FREDRICKSON. Yes, sir. There are a few clouds but I think most of it is sunshine.

Mr. PATTEN. I have no point to make. I am just glad to hear it.

Tell me, we used to get a chart of the organization command with all the new names, is that still available?

Dr. FREDRICKSON. It certainly is, Mr. Patten. We will see you are supplied with the recent one.

BICENTENNIAL ACTIVITIES

Mr. PATTEN. Tell me, we are going to have millions of visitors for the Bicentennial, what are you doing? How can people know anything about you? In the first place, you are 12 miles or so out of town. Do you have a little plan to let the American people know you are there?

Dr. FREDRICKSON. You bet we do, Mr. Patten. We have a visitors' center. We have an organized program, we welcome people. On the 1st and 2d of May of this year we are going to have an open house. Last year we had 30,000 people from this area come, and we would be delighted to have you or any of the members of this committee join us then or at any time. We do have a program hooked up with the Bicentennial. We want the American people to know what NIH is doing for the people.

INTERNATIONAL COOPERATION

Mr. PATTEN. I think often foreigners ask us for guidance and when we go to foreign places we may be taken to that dried-out area in Africa and the problem they hit when they get in there, the little villages with those dying of thirst and malnourishment. I am just wondering. Say we have a boat basin down here testing boats and in Africa they will fight to get such boats. I thought they knew everything about boats but the underdeveloped nations I am surprised to see are interested in this. They don't have such a facility. Have any foreign countries asked you to use your computer? To use your animals? To use your scientists from Canada or Israel or Scotland? Do you have any international cooperation in NIH?

Dr. FREDRICKSON. Numerous ones and growing all the time. I think they are particularly interested in our technology and our assistance in terms of people. We have expanding numbers of agreements with many countries. We have a big program with the U.S.S.R., with Japan, with most of the Western European countries. Through the WHO we are going to increase our assistance to the developing nations in regard to fighting tropical diseases. We have a tremendous amount of expertise and knowledge to export. We increase these activities as we can, compatible with our resources and our ability to do so.

I think we are linked around the world in one large biomedical research community where the language is really basically the same and the needs are certainly the same.

NIH is extraordinarily well known around the world, Mr. Patten. It is a great illustration of what America can do, and I think we can be very proud of it.

Mr. PATTEN. I am not downgrading you, because one time I got ahold of Dr. Stetten and those people don't want to go to the White House or the Washington Monument. They said, "We want to take a run out to NIH." They just raved about the time they had out there. By and large we never think of it. We show them the FBI Building. I didn't know if you were in on this. But you see you are.

I have no further questions, Mr. Chairman.

Mr. FLOOD. Mr. Roybal.

CANCER INSTITUTE APPROPRIATION

Mr. ROYBAL. Thank you, Mr. Chairman. I would like to understand a little better what is happening to the Cancer Institute since you are not asking for an increase in funds. What is happening to their research program, how is it being affected?

Dr. FREDRICKSON. Yes, Mr. Roybal. Under the 1977 budget in comparison to the new 1976 appropriation, there will have to be a decrease in a certain number of cancer activities. The Institute itself sees these activities as probably showing the largest change in construction and in the cancer control program. By largest I mean proportional changes relative to the base, a fraction of the budget now devoted to these activities.

Mr. ROYBAL. Cancer control means what?

Dr. FREDRICKSON. The cancer control program is a separate authorization under the National Cancer Institute's budget, which attempts to deal with dissemination. Control programs take certain developments in diagnosis and in treatment and tests ways of sending that information out beyond the cancer centers or using a whole population of a city to see if the population can be saturated with regard to information.

Mr. ROYBAL. That is a very important phase of the program, is it not?

Dr. FREDRICKSON. It is an important phase. Yes, it is.

Mr. ROYBAL. That is being curtailed because you are not requesting any more funds?

Dr. FREDRICKSON. Relatively speaking, their projection would be about an 8 percent decrease.

Mr. ROYBAL. It is a decrease. Eight percent of how many millions of dollars?

Dr. FREDRICKSON. About $59 million.

Mr. ROYBAL. So it is in fact a substantial decrease, is it not?

Dr. FREDRICKSON. In dollar terms it is, that is correct.

Mr. ROYBAL. What about the outlook to the general public; how much will they be shortchanged by this decrease?

Dr. FREDRICKSON. It is a little difficult to say whether you can debate that in terms of a percentage of population not covered. Perhaps it will mean greater selectivity about what should be the subject of such a program.

Mr. ROYBAL. It seems in this field, particularly in this field, there shouldn't be that kind of decrease. Is there any other program where this decrease could have taken place without jeopardizing this program?

Dr. FREDRICKSON. It lies within the purview of the Cancer Institute to distribute changes in their budget, and I am sure the Director will address that more specifically.

There are a number of other lines. Of course, virtually all of them show some modest decrease due to the increment in the 1976 appropriation that was not in the 1976 base on which the 1977 budget was constructed.

REASON FOR BUDGET DECREASES

Mr. ROYBAL. That is what I am concerned about because I remember last year you were asking for more funds for personnel, and we heard arguments as to why the number of personnel should be increased. Now we find this year you are proposing a decrease, and a layman like myself cannot understand this, particularly when it is affecting an area that, at least in my opinion, is so important.

Dr. FREDRICKSON. Yes, I understand, Mr. Roybal.

Mr. ROYBAL. Can you explain to me in layman's language why this is necessary?

Dr. FREDRICKSON. A decrease in the overall budget is necessary.

Mr. ROYBAL. Do you recommend I believe that?

Dr. FREDRICKSON. It is in terms of the constraints of the total 1977 figure for NIH with which we dealt.

Mr. ROYBAL. I understand that, but do you believe it? It seems to me what you are telling me is that your heart is not in it. I hear what you say. I just don't feel that it is said with conviction.

Dr. FREDRICKSON. I think, Mr. Roybal, within this total figure, I feel very confident of the distribution we have produced for you. This is where I would put my emphasis and not change it.

Mr. ROYBAL. I think I understand what you are saying. Within the limits that you have to operate, the distribution that is being made is satisfactory.

Dr. FREDRICKSON. I think it is, yes, sir.

Mr. ROYBAL. It is better than nothing, in other words?

Dr. FREDRICKSON. Yes.

Mr. ROYBAL. I think we have come to the conclusion, then, there is a decrease?

Dr. FREDRICKSON. Yes, there is.

Mr. ROYBAL. Is less money being spent on this subject matter? I think we both agree that it is important.

Dr. FREDRICKSON. Yes, I think there are many items that are very important here, sir.

NATIONAL INSTITUTE ON AGING

Mr. ROYBAL. I see that you have a budgeted item of $26.2 million for the National Institute on Aging. Is that an increase?

Dr. FREDRICKSON. That is an increase over their budget this year of approximately $19 million, which in turn was raised from around $16 million last year. But this is a new institute, Mr. Roybal. It is just beginning to accelerate and that appropriation therefore has a larger percentage increase than any other.

Mr. ROYBAL. But the Institute itself is increasing its activities, is it not?

Dr. FREDRICKSON. Yes, it is.

Mr. ROYBAL. In which way is it being increased?

Dr. FREDRICKSON. In several ways. It is going to increase its intramural program which is located in Baltimore, and it will begin to look at areas that it thus far has not been active in. That is, it will be doing more not only in the question of what the aging process is, which is a very important biomedical problem, but about the diseases of aging people. For example, it will be expanding a study it has made of males over many, many years to women so they, too, will be included.

It will also be engaged in more studies, of a kind relatively new to NIH, in some of the social sciences relative to the problems of the aging—the problems that are particular to that large and important population.

It will, for the first time, be looking at the problem of aging with a broader perspective than was possible when they were a part of the National Institute of Child Health and Human Development. The total program for Federal research in aging is being examined under a plan, that is now in progress, in which the Council of this new Aging Institute has a major helping hand, to integrate the total effort in aging research being made by all Federal agencies.

Mr. ROYBAL. This is in a long-range program?

Dr. FREDRICKSON. Yes, indeed it is. It is a very serious effort to get into the aging problem both medically, biochemically, and to a certain extent socially and economically.

MINORITY STAFF AT NIH

Mr. ROYBAL. I think that satisfies Mr. Patten; I know it does me.

I have one other subject matter and that is that a statement was made that the morale of the staff is excellent. Does that also include members of minority groups working within NIH?

Dr. FREDRICKSON. I think it does. NIH is very conscious of its responsibilities under the Equal Opportunity Act.

Mr. ROYBAL. Why hasn't it implemented the act? Six-tenths of 1 percent of all the employees have Spanish surnames, as an example.

Dr. FREDRICKSON. I am aware there are very few.

Mr. ROYBAL. The number of members of minority groups as a whole is much lower than the vast majority of Government agencies and institutions.

Dr. FREDRICKSON. I am not sure that it is, Mr. Roybal, but I certainly don't mean to dispute you.

Mr. SCHWARTZ. Our percentage of black employees at NIH is equal to the percent of blacks in the metropolitan Washington area.

Mr. ROYBAL. I am just talking about the percentages as they relate to the national average.

Mr. SCHWARTZ. As related to the national average, we are well in excess. I think our major problem, Mr. Roybal, is in terms of average grade of our minority employees. That is the thing that needs the most correction. The numbers are at least consistent with the metropolitan area but we are working very hard to enable these people, through upward mobility programs and training programs, to move into more professional jobs.

UPWARD MOBILITY PROGRAM

Mr. ROYBAL. You anticipated my next question. I wanted to find out why there was no real upward mobility effort being made with regard to black Americans, but I am particularly interested in why we have a 0.6-percent average of Spanish surnames employed at NIH.

Mr. SCHWARTZ. I think your observation is quite correct, Mr. Roybal. We are in the process of hiring a Spanish-surnamed coordinator. I might add that one of our main advocates to insure that our performance improves is Dr. Fredrickson's secretary. She is Spanish-surnamed and keeps track of us quite closely.

I would like to put in the record, Mr. Roybal, the upward mobility programs that we have. We are quite proud of them. We think they are quite extensive. We think they are working, and I would like to embellish that.

Mr. ROYBAL. I would appreciate if you would.

[The information follows:]

UPWARD MOBILITY PROGRAMS

The upward mobility program of the National Institutes of Health is comprised of five structured programs:

(1) Stride, a program providing a combination of academic education and on-the-job training leading to placement in previously identified professional positions (74 current participants); (2) upward mobility college, an on-site academic program offering work related and general development courses to NIH employees (250 current participants); (3) Worker trainee opportunities, a training program for disadvantaged workers entering the Federal work force (21 current participant); (4) Clerk-typist career development program, a program providing clerk-typist training to competitively selected lower level employees resulting in their placement as clerk-typists at the NIH (10 current participants); and (5) Individual new careers training, a program providing on-the-job training to placement in new career fields for lower level employees competitively selected for the opportunity (eight current participants). These programs provide a variety of developmental opportunities for the approximately 5,000 employees in the NIH target population, GS–7 and below and Federal wage system equivalents of the National Institutes of Health. The target population is composed of 74 percent women and 26 percent men, 33 percent minorities and 67 percent nonminority. Minority women represent 20 percent of the total target population. Thirteen percent of the target population are minority males.

In the period from June 1972 through December 1975, 164 nonprofessional employees have been competitively selected from the target population for training and education leading to placement in professional positions through the NIH Stride program. Of this group 55 have completed the program and are placed in target professional positions. Approximately 90 employees are con-

tinuing in various stages of training and education. Current plans include announcing up to 50 new opportunities to be filled in fiscal year 1977. Graduates of the stride program are currently working at NIH as registered nurses, biologists, accountants, personnel specialists, technical information specialists, statisticians, computer programers, management analysts, administrative assistants, contracts specialists, and public information specialists.

An outgrowth of upward mobility programing (such as described above) is the NIH manpower projection process initiated in 1973. This process forecasts NIH's ability to absorb program graduates in the occupational areas for which they will be trained. Training opportunities are determined by this process to assure placement upon completion of training.

In an effort to assist target population employees in establishing realistic career goals based on the best occupational forecast data available, the NIH has initiated a career proposal workshop. This workshop allows employees to determine and explore their personal career objectives within the context of NIH's manpower projections and program opportunities. Assistance is available to employees from guidance and counseling staff, career development staff as well as occupational specialists in the various occupations of the NIH. Since May 1974, over 200 employees have participated in this workshop and developed formal career proposals relative to their career goals at NIH.

The NIH upward mobility college since its beginning in 1972, has provided academic education to approximately 1,250 employees from the target population. Twenty-nine achieved associate of arts degrees and 13 have achieved baccalaureate degrees in this program.

Mr. ROYBAL [continuing]. I know for a fact that the average is quite good with regard to the black population in Washington, D.C., and also good with regard to the overall U.S. population of blacks. On the other hand, the upward mobility program, in my opinion, leaves a lot to be desired.

Finally, with regard to my remark of a few moments ago, as to the Spanish-speaking, the percentage employed at N.I.H. is 0.6. This is one of the lowest percentages of any department in the Federal Government.

Mr. SCHWARTZ. I think you are quite correct. We will try to get at it by having an individual working full time trying to improve recruitment and promotion opportunities.

Mr. ROYBAL. I asked these questions of other departments. I don't know whether I have heard that before from you, but I have heard it from other departments: We are going to see if we can do something about it. But then the next year nothing is done. I hope I return to this committee next year because I am going to ask the same question next year.

CANCER AND HEART DISEASE RESEARCH

Mr. FLOOD. Mr. Michel, you have some additional questions?

Mr. MICHEL. I confined my earlier questions to the whole grant procedure but let me conclude, if I might, with several in this area of the institutes and the relationship of making up that whole figure. Doctor, you are in charge of the whole NIH. While it has a reduction, there has been considerable furor here over the marked reduction in cancer, and isn't there some in heart too? Now, both of those institutes came in for exceptionally big increases in the last several years, I guess due to the diseases being No. 1 and 2 death causes and because of the resultant pressures individual members get.

In the Cancer Institute while we will get a chance to develop that more fully when Dr. Rauscher is here, does this reduction in figure here as far as you are concerned mean that any of those ongoing research programs are going to be cut back?

Dr. FREDRICKSON. Yes, I think it will, Mr. Michel. I think that we can use more funds for some of these programs.

Mr. MICHEL. Does it permit any new research grants at all?

Dr. FREDRICKSON. Oh, yes; it does.

Mr. MICHEL. How does it do that?

Mr. PATTEN. That is a negative increase.

Mr. MICHEL. No. I am serious about that because it goes back to my first line of questioning with respect to continuing grants and new competing ones, and I think we equate things too many times simply with dollars and cents rather than results. You get too much money available and you get some pretty questionable applications for grants at times in my opinion. Even in this field, where everybody is afraid to tread on cancer research, you just can't be opposed to it. It is too critical a thing and it is too touchy a subject to deal with with your constituents. But I don't want to go on that floor and the first thing out of a box is a quarter of a billion increase in one item and then we get whipsawed in others because you did it for one; you are going to compound it and do it for the others.

Before long we have a bill that is a billion and a half over the budget and we are right back in the same old box again. Isn't there anything in cancer research being done down here in the Environmental Institute? Is there anything being done in cancer research in General Medical Sciences?

Dr. FREDRICKSON. Yes, there are.

CANCER RESEARCH IN OTHER INSTITUTES

Mr. MICHEL. Is there anything being done in cancer research in the the General Medical Sciences Institute?

Dr. FREDRICKSON. Yes, sir.

Mr. MICHEL. How about some of these other Institutes; isn't there cancer research in those other institutes?

Dr. FREDRICKSON. Yes, there is cancer research.

Mr. MICHEL. Why didn't you step forward, then, and lay out a little bit of what some of these other institutes are doing in the area of cancer research or in heart and lung so that you don't put us in this doggoned box that I see myself getting put into here. It ought to come out a little bit more hardline, because that is the case.

If you were to read this record, minus what we have just had in this brief exchange you would think, for heavens sake, there are no increases in any other area in cancer research, and it ought not to be left that way. So will you please fill out the record here as to what is being done in cancer research in these other institutes.

Dr. FREDRICKSON. We will add to the record, Mr. Michel, in that regard.

[The information follows:]

CANCER RELATED RESEARCH

The progress that is made against any given disease or group of diseases is generally derived from fundamental research efforts which deal broadly with a wide array of normal and abnormal life processes. Thus the research conducted or supported by a given institute of the NIH may have relevance not only to its

range of categorical disease interests, but also to the more diverse categorical interests of other institutes. It is estimated that $63.6 million worth of research, strongly or possibly related to cancer is being done by other institutes at NIH. It should also be recognized that approximately 50 percent of the NCI appropriation supports basic research which has relevance to the diverse interests of other NIH institutes. In fiscal year 1976 the NCI will provide $23 million to OD–NIH as its portion of the NIH Management Fund and an additional $7 million to other components of the NIH for direct support of cancer related activities.

The specific fields of study in the institutes, as well as a table showing their cancer-related research dollars, follow:

National Heart and Lung Institute: The relationship of the treatment of cardiovascular diseases and various cancers; leukemia research.

National Institute of Dental Research: The early diagnosis, treatment and prevention of oral cancers.

National Institute of Arthritis, Metabolism and Digestive Diseases: The relationship of nutrition and cancer; pancreatic cancer; relationship of cancer and pituitary function.

National Institute of Neurological and Communicative Disorders and Stroke: Research on brain tumors and other tumors of the nervous system.

National Institute of Allergy and Infectious Diseases: Immunology research; virology as it relates to cancer; studies to control infections which affect cancer patients.

National Institute of General Medical Sciences: The role of genetics in cancer causation; basic biology and biochemistry of cells.

National Institute of Child Health and Human Development: Studies on the carcinogenicity of oral contraceptives, analgesics, diethylstilbestrol; clinical studies on juvenile osteosarcoma, prostatic cancer and acute leukemia.

National Institute on Aging: The relationship of the immune response systems of the aging and cancer; basic research on cell culture systems.

National Eye Institute: Research on the biologic behavior of visual disease through the use of intraocular malignancies; changes in the retina induced by herpes and sarcoma viruses in animals.

National Institute of Environmental Health Sciences: Studies on Environmental agents that cause cancer, that is asbestos, granite dusts, fiberglass and polyurethan dusts, vinyl chloride, food and food additives, x-rays, radioactive substances.

NIH cancer related research, fiscal year 1976 appropriation level

	Thousands
NHLI	$700
NIDR	452
NIAMDD	5,565
NINCDS	650
NIAID	[1] 39,000
NIGMS	7,940
NICHD	1,400
NIA	3,021
NEI	635
NIEHS	4,200
Total	63,563
NCI	761,727
Grand total	825,290

[1] Of this amount $32,600,000 will be obligated for basic studies in cell biology and in immunology related to infectious diseases such as influenza and the common cold. The results of some of these studies could very well provide information applicable to cancer.

Mr. MICHEL. Very well.

Mr. FLOOD. Mr. Conte.

POSTDOCTORAL FELLOWSHIPS

Mr. CONTE. Will the emphasis be on postdoctoral fellowships under National Research Service Awards again this year?

Dr. FREDRICKSON. Yes. The administration position would limit new awards by NIH in fiscal year 1976 to individual fellowships, which at NIH are awarded for postdoctoral research training only.

Mr. CONTE. How many of these awards do you expect to make?

Dr. FREDRICKSON. The administration's position would allow NIH to make up to 1,100 new individual fellowship awards. But assessment of expectations for fiscal year 1976 must allow for two contrasting outcomes. Renewal of appropriation authority for the National Research Service Award Act followed by a supplemental appropriation would allow funding of some part of the 2,000 individual fellowship applications received in January of this year. In the absence of renewed authority, the continuing resolution provides for funding at a level corresponding to 80 percent of the fiscal year 1975 level, an outcome that would reduce the number of new awards to a very small fraction of the allowed 1,100.

INSTANT CONSULTATION

Mr. CONTE. I am interested in your system for "instant consultation" with some knowledgeable person at, I assume, NIH. Could you explain how this would work?

Dr. FREDRICKSON. We are in the process of setting up a system in cooperation with the University of Wisconsin Medical Center to expand a "cancer consultation network" to include the full range of disease problems. All physicians in the State will be able to call the program center toll free and through it be connected promptly with a member of the panel of specialists at the medical school.

Mr. CONTE. What stage is this system currently in?

Dr. FREDRICKSON. Informal arrangements have been made with the University of Wisconsin Medical Center to provide the panel of experts available for telephone consultation. Funds have been set aside to add personnel and facilities to the Cancerline Center in Madison. We hope to have the system in operation by midsummer.

Mr. CONTE. How expensive would the television network hookup you describe in your opening be?

Dr. FREDRICKSON. At this stage we are proceeding along two paths toward making use of television as a means for improving information dissemination to practicing health professionals.

The National Library of Medicine's Lister Hill National Center for Biomedical Communications is setting up a limited network of two-way centers which will use the recently launched Communications Technology Satellite. These experiments will concentrate on the use of the network for two-way conferences, consultation, and data transmission between widely separated points across the country. The satellite itself is financed jointly by the Canadian Government and NASA.

The NIH expenditures of approximately $2 million will be used to establish and operate the ground stations for 1 year.

To carry out our planned use of the satellite for one-way transmission of continuing education programs from NIH to health practitioners will require the establishment of receiving centers at key points, particularly at the originating stations of statewide and regional networks. The receiving installation will cost from $20,000 to $30,000 each. We tentatively plan to start with six such receivers. We

estimate that installation and organizational costs will be about $250,000, and that the NIH share of maintenance and operation of the network for continuing education will amount to $250,000 per year.

As a preliminary step, before expenditures for installation and operation of the continuing education network, we will produce a few pilot programs and test them for effectiveness on existing medical education television networks. The sum of $100,000 has been set aside for this purpose.

Obviously, the eventual cost of the television activity will depend upon the number of ground terminals set up and the volume of program material presented.

The equipment and technical operation costs, as I have indicated, are estimated at $2 million for a one-time expenditure, with an operation cost of $600,000 per year.

We do not have a firm estimate of program costs. This will be in much better focus after our pilot program tests for which we are spending $100,000.

AMBULATORY CARE RESEARCH FACILITY

Mr. CONTE. What is the status of the construction project at Lister Hill Library Building?

Dr. FREDRICKSON. The working drawings for the building have been completed, and the environmental impact statement is under review and expected to be completed within the next several months.

Mr. CONTE. Do you feel that the proposed ambulatory care research facility will help to increase the number of outpatients who now must be inpatients?

Dr. FREDRICKSON. The Clinical Center currently has a total of 519 beds available for inpatients. Most of the bed patients are hospitalized for long periods of time which reduces the total number of patients who can be treated during any one period. With better facilities for outpatients, the number of patients who can be treated can be greatly increased.

Mr. CONTE. How much could this facility increase the outpatient visits per year?

Dr. FREDRICKSON. The new facility would permit outpatient visits to be increased from the current total of 60,000 each year to approximately 200,000.

Mr. CONTE. If you intend to wait until the ambulatory facility is completed to reassess the need for a Child Health Institute, can you tell us how long it will take?

Dr. FREDRICKSON. The design has been completed for the research facility for the National Institute of Child Health and Human Development. This project has a high priority for construction funding and is unrelated to the need for the ambulatory care facility.

BUDGET ALLOCATION

Mr. CONTE. Do you feel in your professional judgment that the allocation of funds between the various component institutes at NIH is the best and most profitable one possible?

Dr. FREDRICKSON. I do. As I said earlier, when the budget for 1977 was constructed, we allocated the increase over the 1976 base in a

manner that gave the largest percentage increases to the Institutes where we thought the need was greatest. I was satisfied that the resultant budget made a sound disposition of the total funds available to NIH.

The subsequent enactment of the vetoed appropriations bill, which included substantial increases for fiscal year 1976 for some of the Institutes, has, of course, altered the percentage increases. In fact, some of the increases we thought we were asking for have now become decreases. In those cases, the Institute concerned, instead of having additional funds in fiscal year 1977, as we intended, will have to adjust to a decrease in funds next year. In most cases, however, the actual increase in fiscal year 1977, over the actual appropriation for fiscal year 1976, will merely be somewhat smaller than it would have been over the fiscal year 1976 level at which we thought we would be operating when the budget was constructed.

So, the situation is somewhat different from what I had expected it to be. However, when looked at relative to each other, the amounts requested are not significantly out of line with my judgment or intentions.

Mr. FLOOD. Thank you very much, gentlemen. We will move on to our first institute tomorrow morning.

MICHEL PEER REVIEW QUESTIONS

We will also insert in the record at this point a set of materials prepared by NIH for Mr. Michel on NIH peer review activities.

[The information follows:]

Mr. MICHEL. I think you ought to provide for the record your most recent list of review panels with the names of the people who serve on each panel and the institutions they come from.

Dr. FREDRICKSON. This information is published twice each year in a book called "NIH Public Advisory Groups." It runs to more than 300 pages which may be too bulky to insert in the record but I will certainly submit copies for the information of the committee.

Mr. MICHEL. Also indicate the dates they met and the total number of grants they approved on those dates.

Dr. FREDRICKSON. I shall be glad to submit that for the record.

(CLERK'S NOTE.—This information has been supplied and is available in the committee's files.)

Mr. MICHEL. Do any of these peer reviewers receive research grants or contracts from NIH?

Dr. FREDRICKSON. Yes, Mr. Michel, most of them do. This is inevitable as we try very hard to get the best possible scientists, who are fully conversant with the present state-of-the-art in their field, to serve on these review groups. They must have demonstrated their ability as established, independent research investigators and, as such, they are likely to be successful competitors for NIH grants. As NIH is the major source of support for biomedical research in nonprofit institutions, most of the best qualified investigators in these institutions are NIH grantees. They do not, of course, sit in judgment of their own grant applications.

Mr. MICHEL. Do they participate in the review of grant proposals submitted by others from their own institutions?

Dr. FREDRICKSON. No. Members of review groups are required to be absent during the discussion of applications from their own institutions. They may not vote on such applications and do not receive these applications for review. This NIH policy also applies to advisory councils and boards as well as the Study Section and other initial merit review groups. Applications from a member of a review group must be reviewed by a different group, and by a different executive secretary.

Mr. MICHEL. What is the total cost for administering the peer review system? This should include travel, per diem, consultant fees, secretarial assistance—in other words, the whole gamut of expenditures.

Dr. FREDRICKSON. The cost of operating the Study Sections in the Division of Research Grants in 1975 was $6 million. That includes costs for consultant reviewers and site visitors, the DRG staff and processing costs. That accounts for the review costs for 14,600 grant applications. The cost for reviewing the 2,000 applications reviewed by Institute committees is proportionately about the same, say, $850,000. The total cost of review for scientific merit is therefore a little less than $7 million. This represents about one-fifth of 1 percent of the amount of money requested in the grant applications.

Mr. MICHEL. What kind of a grant monitoring system do you have to insure that the intended research is being pursued and accomplished?

Dr. FREDRICKSON. NIH has developed several techniques for assuring the continued scientific quality and focus on the original objectives during the years of committed support. There is a requirement for submission of a progress report each year when the request for the next year's funds is made. There are a number of other devices for monitoring, particularly for the large grants, the most common of which is site visits by NIH staff, usually accompanied by Council members or other appropriate consultants, in the second or third year of the project period. For center grants, we usually require local scientific or administrative advisory groups, frequently both. There are also annual, and sometimes more frequent, meetings of all program directors and primary research staff of centers devoted to a given scientific or disease area, to discuss scientific and management problems. Reports on these meetings are disseminated to the field, if they include matters of general interest.

A more general type of monitoring includes conferences with national scientific and professional organizations involved in particular research problems or fields. There are also special omnibus peer reviews of all projects and progress in specific program areas and reports on these reviews are subsequently disseminated to all investigators working in the program area.

Mr. MICHEL. How many separate review panels do you have?

Dr. FREDRICKSON. Most of the reviewing of grant applications received at NIH is done centrally by the Division of Research Grants which was set up for this purpose 30 years ago when NIH first started making grants. Panels of experts, which we call Study Sections, are set up to cover the relevant scientific disciplines and medical specialties and the number of these bodies fluctuates in accordance with requirements. The Division of Research Grants at present has 52 Study Sections which review grants for scientific merit and assign priority scores to those they recommend for approval. These grant applications are simultaneously assigned to the relevant Institute by the Division of Research Grants. After the Study Sections have completed their reviews, the applications are examined by the Institute for program relevance. Those whose scientific merit has earned them the approval of the Study Section are submitted to the Institute's National Advisory Council, which is a statutory body, for final approval. As you know, only those applications recommended for approval by such an advisory council—or, in the case of the Library of Medicine, its Board of Regents—are eligible for award. To the extent that funds are available, that is.

A relatively small number of grant applications in very specialized fields of particular program interest, including applications for so-called program projects and research center grants, are reviewed not by the DRG Study Sections but by special initial review groups—similar in composition and function—established on an ad hoc or semipermanent basis within the Institute. Four of the Institutes and the Library of Medicine each have one such grant review group; four of the Institutes have three to five; the highest number is in the Cancer Institute which has nine; and two Institutes have none. Altogether, there are 29 such groups. I will submit a list of them for the record.

I should, perhaps, emphasize that, to the maximum extent that staff and related resources permit, review is conducted in the Institutes by offices that are separate from those responsible for program development. The Division of Research Grants closely monitors all NIH review groups so that the standards and quality of review are as uniform as we can make, no matter where the initial review takes place.

[The information requested follows:]

National Cancer Institute (9) :
- Cancer Clinical Investigation Review Committee
- Cancer Control Grant Review Committee
- Cancer Research Center Review Committee
- Cancer Special Program Advisory Committee
- Clinical Cancer Education Committee
- National Bladder Cancer Project Working Cadre
- National Large Bowel Cancer Project Working Cadre
- National Pancreatic Cancer Project Working Cadre
- National Prostatic Cancer Project Working Cadre

National Heart and Lung Institute (5) :
- Arteriosclerosis Specialized Centers of Research (SCOR) Ad Hoc Review Committee
- Comprehensive Sickle Cell Centers (CSCC) Ad Hoc Review Committee
- Pulmonary Specialized Centers for Research (SCOR) Ad Hoc Review Committee
- Pulmonary Young Investigator Grant Committee
- Thrombosis Specialized Centers of Research (SCOR) Ad Hoc Review Committee

National Institute of Dental Research (1) : Dental Research Institutes and Special Programs Advisory Committee

National Institute of Arthritis, Metabolism, and Digestive Diseases (none) :

National Institute of Neurological and Communicative Disorders and Stroke (3) :
- Communicative Disorders Review Committee
- Neurological Disorders Program-Project Review A Committee
- Neurological Disorders Program Project Review B Committee

National Institute of Allergy and Infectious Diseases (1) : Allergy and Immunology Research Committee

National Institute of General Medical Sciences (1) : Minority Access to Research Careers Review Committee

National Institute of Child Health and Human Development (3) :
- Maternal and Child Health Research Committee
- Mental Retardation Research Committee
- Population Research Committee

National Institute of Environmental Health Sciences (none)

National Eye Institute (1) : Vision Research Program Committee

Division of Research Resources (4) :
- Animal Resources Advisory Committee
- General Clinical Research Centers Committee
- General Research Support Program Advisory Committee
- Primate Research Centers Advisory Committee

National Library of Medicine (1) : Biomedical Library Review Committee

Mr. MICHEL. About how many grants, on the average, do they review and approve?

Dr. FREDRICKSON. In fiscal 1975, 16,691 grant applications were reviewed. The Division of Research Grants provided the initial merit review for 14,606—that's nearly 90 percent of these grant applications. As there are 52 Study Sections, that is an average of—let me see—290 applications each. The other 2,085 applications were reviewed by the 29 Institute groups; that would be an average of about 70 for each group. However, the review load varies widely. Some review committees deal with only a small number of highly complex center grant applications; at the other extreme, a few Study Sections must cope with more than 400 applications a year. When the load gets too large, we try to create a second Study Section to take half of the applications, if we have the funds and the personnel slots for the necessary ancillary staff. We now have two Study Sections simply labeled A and B—for such fields as surgery, neurology, biophysics and several others. Another device for keeping the load within reason is to split the function between two Study Sections, such as replacing the Cardiovascular Study Section with a Study Section for Cardiovascular and Pulmonary Diseases and another for Cardiovascular and Renal Diseases. Actually, Mr. Michel, a workload of 400 applications a year is too much; that means that some 135 long and often technical complex applications have to be reviewed and analyzed by each Study Section member before each meeting. If such demands are maintained for very long, the quality of review is bound to suffer.

Mr. MICHEL. Who selects the members of these panels?

Dr. FREDRICKSON. Nominations to fill vacancies on an initial grant review group are first proposed by the executive secretary of the group—who is a mem-

ber of the NIH staff—in conformity with detailed criteria and guidelines for such nominations. They also consult a variety of sources both within NIH and in the scientific community for suggestions and recommendations. An executive secretary's nominations are reviewed by the Director of the bureau, institute or division responsible for the committee. The Director, of course, may approve or change these nominations. Final appointment is by the Director, NIH, after administrative review by the NIH Committee Management Officer.

Mr. MICHEL. Where do the individuals selected normally come from?

Dr. FREDRICKSON. Most of the members of these review groups come from medical and other health professional schools, research hospitals, university departments. A few are scientists in Federal employ. We use the best experts wherever we can find them.

Mr. MICHEL. What are the basic criteria that are used to govern the selection of these individuals?

Dr. FREDRICKSON. The principal and all-important criteria are: First, recognized achievement in a relevant field—to judge the scientific merit of proposals the reviewer must have high professional competence and first-hand knowledge of the subject matter and, to insure credibility and acceptance by the scientific community, his qualifications and achievements must be recognized by his peers; second, mature judgment and objectivity as a scientist, in order to insure a balanced perspective; and third, ability and willingness to serve—as the task is very demanding, the candidate must be able to work effectively with a group, must accept responsibility for doing the necessary homework, and must be available to attend the group's meetings and, as necessary, to participate in site visits.

Perhaps, I should add a fourth quality—though it is implicit in the second—and that is the tact, discretion and restraint to protect the confidentiality of an applicant's ideas and the reviewers' opinions.

It is also important that all the necessary scientific disciplines or clinical specialties be represented on a review group, with a proper balance of subspecialization within those fields, so that the skills of the reviewers will fully encompass the range of applications to be reviewed.

Finally, there are some more or less mechanical requirements: We do not permit two members of the same institution to serve on the same panel; we do not appoint full-time employees of profitmaking organizations; and we don't let members succeed themselves on the same review group. We also aim for reasonable geographic distribution of membership and for equitable representation for women and minorities but these considerations are secondary to our search for the highest caliber people we can find.

Mr. MICHEL. Do any of these individuals sit on more than one panel?

Dr. FREDRICKSON. No, sir, it is a firm NIH policy that no person may serve simultaneously on more than one initial review committee.

Mr. MICHEL. What kind of reimbursement do they receive?

Dr. FREDRICKSON. They are paid at the rate of $100 per day for time spent at meetings, plus per diem and travel expenses, in accordance with standard government travel regulations—except, of course, for full-time Federal employees. No reimbursement is paid for the considerable time they spend reviewing the applications at home in preparation for each meeting.

JUSTIFICATION OF THE BUDGET ESTIMATES

Appropriation Estimate

Biomedical Research

For carrying out, to the extent not otherwise provided, titles III, IV, X, and XI of the Public Health Service Act, $2,139,647,000, 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; Provided, That none of these funds shall be used to pay recipients of general research support grants programs any amount for indirect expenses in connection with such grants. 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 thirteen passenger motor vehicles for replacement only. (Additional authorizing legislation to be proposed for $69,830,000.) 1/

Explanation of Language Changes

1/ The proposed language presents a single appropriation for all activities of the National Institutes of Health (excluding construction) formerly carried in fifteen separate appropriations.

Obligations by Account

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Appropriation by account:								
National Cancer Institute	1,887	$688,314,000	1,968	$762,647,000	1,887	$687,670,000	-81	-$74,977,000
National Heart and Lung Institute	704	305,036,000	747	370,347,000	704	342,855,000	-43	-27,492,000
National Institute of Dental Research	269	48,728,000	282	51,427,000	269	52,207,000	-13	+780,000
National Institute of Arthritis, Metabolism, and Digestive Diseases	560	162,128,000	588	179,801,000	560	180,837,000	-28	+1,036,000
National Institute of Neurological and Communicative Disorders	511	135,400,000	543	144,707,000	511	146,532,000	-32	+1,825,000
National Institute of Allergy and Infectious Diseases	587	119,447,000	621	127,163,000	587	135,615,000	-34	+8,452,000
National Institute of General Medical Sciences	153	167,614,000	164	187,388,000	153	193,435,000	-11	+6,047,000
National Institute of Child Health and Human Development	354	122,343,000	377	136,573,000	354	129,883,000	-23	-6,690,000
National Institute on Aging	173	16,171,000	193	19,388,000	173	26,220,000	-20	+6,832,000
National Eye Institute	141	44,508,000	152	50,285,000	141	46,950,000	-11	-3,335,000
National Institute of Environmental Health Sciences	238	34,143,000	271	37,780,000	238	46,141,000	-33	+8,361,000
Research Resources	74	83,411,000	77	130,300,000	74	92,342,000	-3	-37,958,000
John E. Fogarty International Center for Advanced Study in the Health Sciences	50	5,393,000	51	5,694,000	50	7,492,000	-1	+1,798,000
National Library of Medicine	468	29,456,000	472	29,244,000	468	35,234,000	-4	+5,990,000
Office of the Director	546	15,325,000	546	15,325,000	546	16,234,000	....	+909,000
National Institutes of Health Management Fund	3,301	.....	3,353	.....	3,183	.....	-170	.....
Service and Supply Fund	644	.....	767	.....	762	.....	-5	.....
Total, Biomedical Research, NIH	10,660	1,977,417,000	11,172	2,248,069,000	10,660	2,139,647,000	-512	+108,422,000

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

Biomedical Research

I. Fiscal Year 1977 Budget

The budget for the National Institutes of Health (NIH) is presented as a single appropriation request instead of separate proposals for each bureau, institute, or division, as in previous years. The request for funds for construction, repair, and improvement of the research and service facilities are submitted separately. Formerly, the requirements for NIH Biomedical Research required fifteen separate budget schedules. The consolidation of the separate activities streamlines the formulation, presentation, and review of the several components dedicated to the same end product--conquering disease. It provides a review of total NIH funding which tends to be obscure in a multi-appropriation presentation. The functions, responsibilities, and authorities of the organizational components of NIH are in no way diminished or compromised by such a submission.

To provide continuity, a detailed justification is presented for each organizational component, however, we are requesting a single appropriation for the National Institutes of Health.

The Fiscal Year 1977 budget request reflects the funds needed to continue support of on-going productive research efforts; to pursue Congressionally mandated research priorities with respect to arthritis, diabetes, sudden infant death syndrome, aging, and the potential environmental hazards related to sulphur oxide, polyvinylchloride (PVC), and asbestos; and to deal with other program priorities. Outlined below are some of the major issues taken into account in the funds requested:

- Funds have been allocated to permit a balanced distribution of research funds, especially in view of the emphasis being given to research on cancer.

- The National Institute on Aging will become a functional and viable organization.

- Funds are provided to expand environmental health research, including the development of sensitive and rapid physiological indicators of early environmental damage to man.

- A general research priority will continue to be the knowledge needed to support the development of preventive medicine.

II. Basic Assumptions

The basic goal of NIH is developing knowledge of the biological bases of health and disease and of safe and effective interventions to prevent, detect, diagnose, and treat disease.

In order to achieve this goal, NIH has responsibility for five interdependent types of activity:

- expanding understanding of diseases through biomedical research in laboratories and clinics,

- developing applications of research findings to solutions of health care problems and measures for the diagnosis and prevention of disease,

- testing and evaluating applications through mechanisms such as controlled clinical trials,

- facilitating the transfer of the results of NIH findings to individuals and organizations responsible for health care and prevention through a range of measures, including control and demonstration programs like those in NCI and NHLI,

- developing the manpower, biotechnology, communications, data, and other support resources needed to maintain the above-listed activities.

The interdependence of these activities is significant in the organization of resources to accomplish the basic NIH goal:

- Fundamental research is the source of knowledge about basic life processes upon which successful applied research must build.

- Applied research and development, clinical testing, and demonstration are needed to translate new research knowledge into the interventions of medical practice.

- Manpower and other resource development is needed to take advantage of research opportunities and to meet ongoing research requirements.

- Within the research activities discoveries in one program area contribute to discoveries in other program areas.

- In addition, many discoveries are the consequence of developing a critical mass of research manpower drawn from diverse program areas.

The balance/imbalance among these activities affected by the allocation of resources reflects the interaction of three basic factors:

- research opportunities to be exploited at a given time, including perceptions of the relative state-of-the-art in various problem areas, personnel available, technical developments, and new ideas or information.

- professional and public perceptions of the significance and priorities of different health problems requiring action,

- public values, reflected in legislation, executive action, or judicial decisions and in changing national priorities and organizational arrangements.

III. Background Issues

To the extent that NIH achieves its basic goal, significant assistance can be provided to other agencies in meeting other priority health goals, such as:

- improving the efficacy of medical practice through the validation of knowledge supporting medical interventions,

- improving the assessment of the cost-effectiveness of medical interventions through the development of information about health care outcomes,

- developing systems to effectively identify, monitor, and deal with environmental hazards to human health,

- increasing public awareness of effective disease prevention measures and potential health hazards in personal habits and life-styles.

An effective balance in the organization of NIH programs and activities is essential to the accomplishment of the basic NIH goal. In order to strike such an effective balance, the following issues must be taken into account and dealt with to the extent possible:

- The interface between research and service - involving clinical trial, control, demonstration, and knowledge dissemination activities - involves a determination of the role of NIH in relation to other agencies for translating knowledge into practice. A corollary balance issue is competition for funds and personnel among different components of research activity.

- In order to maintain an effective research effort, resources to provide management options are needed with respect to the recruitment and retention of quality personnel, the level of personnel, the development of required research skills, the updating of facilities to meet research requirements, and the maintenance of stability in the support of research programs.

- Decision and allocation processes need reassessment, especially in view of the decreasing buying power of the research dollar, the basic impact of NIH decisions on the nation's biomedical research effort, and new funding demands as a consequence of legislation creating new commissions and institutes.

DHEW - National Institutes of Health

1976 COLUMN OF 1977 JUSTIFICATIONS

(In thousands)

Appropriation by account:	Research Grants: Regular Program: Non-Comp.	Research Grants: Regular Program: Comp.	Research Grants: Special Programs: Multi-discip. Centers	Research Grants: Special Programs: Other	Training Programs: Grants	Training Programs: Fellows.	Res. & Develop Contrs.	Intra-mural Res. & Direct Opers.	Program Mgmt.	Cancer Control	Cancer Constr.	TOTAL
National Cancer Institute..	$101,351	$56,380	$122,612	$34,099	$5,323	$12,840	$213,173	$128,732	$6,331	$56,806	$25,000	$762,647
National Heart and Lung Institute.....	140,000	68,000	--	6,000	10,539	10,415	87,659	44,734	3,000	--	--	370,347
National Institute of Dental Research.....	14,600	4,304	7,542	647	2,297	3,044	4,908	12,103	1,982	--	--	51,427
National Institute of Arthritis, Metabolism, and Digestive Diseases...	96,762	28,021	4,048	4,740	170	4,174	8,792	32,537	557	--	--	179,801
National Institute of Neurological and Communicative Disorders and Stroke.....	65,000	19,804	7,308	2,532	3,800	4,100	10,835	31,043	285	--	--	144,707
National Institute of Allergy and Infectious Diseases.....	57,417	12,139	--	4,900	3,523	4,411	12,341	32,183	249	--	--	127,163
National Institute of General Medical Sciences.	70,749	40,897	19,681	5,892	22,453	18,398	1,500	7,116	702	--	--	187,388
National Institute of Child Health and Human Development.....	58,328	19,659	5,608	2,066	6,064	3,451	19,754	20,588	1,055	--	--	136,573
National Institute on Aging.....	7,997	1,587	--	99	1,126	636	1,202	6,451	290	--	--	19,388
National Eye Institute.....	26,999	7,487	--	1,017	1,994	2,653	2,322	7,642	171	--	--	50,285
National Institute of Environmental Health.....	11,847	1,780	5,287	249	1,453	292	3,211	13,341	320	--	--	37,780
Research Resources.....	--	--	--	123,256	160	174	3,593	2,525	592	--	--	130,300
John E. Fogarty Internat'l Center for Advanced Study in the Health Sciences...	--	--	--	860	--	--	--	4,834	--	--	--	5,694
National Library of Medicine.....	--	--	--	6,433	--	--	4,000	13,621	5,190	--	--	29,244
Office of Director.....	--	--	--	--	--	--	--	2,221	13,104	--	--	15,325
Total, National Institutes of Health.	651,050	260,058	172,086	192,790	58,902	64,588	373,290	359,671	33,828	56,806	25,000	2,248,069

DHEW - National Institutes of Health

1977 CONGRESSIONAL JUSTIFICATIONS
(In thousands)

Appropriation by account:	Research Grants: Regular Program: Non-Comp.	Research Grants: Regular Program: Comp.	Research Grants: Special Programs: Multi-discip. Centers	Research Grants: Special Programs: Other	Training Programs: Grants	Training Programs: Fellows.	Res. & Develop. Contrs.	Intramural Res. & Direct Opers.	Program Mgmt.	Cancer Control	Cancer Constr.	TOTAL
National Cancer Institute..	$112,844	$21,551	$118,249	$30,667	$1,764	$16,399	$181,384	$135,672	$7,415	$51,386	$10,339	$687,670
National Heart and Lung Institute.....	168,000	26,059	--	5,500	5,152	7,636	82,000	45,908	2,600	--	--	342,855
National Institute of Dental Research.....	17,282	2,694	7,542	691	1,266	1,865	5,408	13,358	2,101	--	--	52,207
National Institute of Arthritis, Metabolism, and Digestive Diseases...	101,980	16,768	5,437	4,586	--	5,883	10,162	35,433	588	--	--	180,837
National Institute of Neurological and Communicative Disorders and Stroke.....	60,126	23,095	9,492	2,757	--	5,341	11,191	34,235	295	--	--	146,532
National Institute of Allergy and Infectious Diseases.....	52,987	22,255	--	5,308	2,000	4,961	13,961	33,872	271	--	--	135,615
National Institute of General Medical Sciences.	99,183	14,482	23,558	5,892	17,620	23,231	1,500	7,256	713	--	--	193,435
National Institute of Child Health and Human Development.....	60,373	12,485	5,608	2,193	3,797	3,548	19,254	21,512	1,113	--	--	129,883
National Institute on Aging.....	6,965	8,268	---	192	659	931	1,642	7,238	325	--	--	26,220
National Eye Institute.....	26,582	4,344	--	1,045	1,187	2,653	2,522	8,437	180	--	--	46,950
National Institute of Environmental Health.....	9,365	8,588	7,210	472	625	1,618	5,000	12,939	324	--	--	46,141
Research Resources.....	--	--	--	85,169	--	365	3,511	2,670	627	--	--	92,342
John E. Fogarty Internat'l Center for Advanced Study in the Health Sciences...	--	--	--	500	--	--	--	6,992	--	--	--	7,492
National Library of Medicine.....	--	--	--	8,000	--	--	6,740	14,700	5,794	--	--	35,234
Office of Director.....	--	--	--	--	--	--	--	2,221	14,013	--	--	16,234
Total, National Institutes of Health.	715,687	160,589	177,096	152,972	34,070	74,431	344,275	382,443	36,359	51,386	10,339	2,139,647

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

Amounts Available for Obligation 1/

	1976	1977
Appropriation	$2,124,006,000	$2,139,647,000
Request pending	124,120,000	---
Subtotal, appropriations	2,248,126,000	2,139,647,000
Real transfer to:		
"Department of State" (For transfer of shared administrative support of NCI overseas field stations)	-23,000	
Comparative transfers to:		
"Salaries and Expenses,"Department of State" CORE costs	-33,000	
"Acquisitions, Operations and Maintenance of Buildings Abroad,State" for CORE costs.	-1,000	
Total, obligations	2,248,069,000	2,139,647,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1975 - $7,141,000; 1976 - $17,928,000.

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	11,154	10,660	-494
Full-time equivalent of all other positions	1,116	1,190	+74
Average number of all employees	11,820	11,948	+128
Personnel compensation:			
Permanent positions	$126,958,000	$130,940,000	+$3,982,000
Positions other than permanent	12,178,000	13,706,000	+1,528,000
Other personnel compensation	4,273,000	4,610,000	+337,000
Subtotal, personnel compensation	143,409,000	149,256,000	+5,847,000
Personnel benefits	19,546,000	20,452,000	+906,000
Travel and transportation of persons	7,083,000	7,390,000	+307,000
Transportation of things	1,049,000	1,207,000	+158,000
Rent, communications and utilities	10,923,000	12,673,000	+1,750,000
Printing and reproduction	4,160,000	4,466,000	+306,000

Other services:			
Project contracts	421,879,000	383,179,000	-38,700,000
Payment to NIH Management Fund	84,257,000	92,473,000	+8,216,000
SLUC	3,310,000	4,298,000	+988,000
Other	69,843,000	71,355,000	+1,512,000
Supplies and materials	38,228,000	40,362,000	+2,134,000
Equipment	13,486,000	14,463,000	+977,000
Lands and structures	7,692,000	33,124,000	+25,432,000
Literature	775,000	875,000	+100,000
Grants, subsidies and contributions	1,431,559,000	1,337,654,000	-93,905,000
Insurance claims and indemnities	1,000	1,000	---
Total, Obligations by Object	2,257,200,000	2,173,228,000	-83,972,000

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
		Comparable		
1967	$990,561,000	$1,025,806,000	$1,055,906,000	$1,055,906,000
1968	1,125,520,000	1,119,694,000	1,176,149,000	1,120,845,000
1969	1,161,934,000	1,115,372,000	1,174,420,000	1,135,660,500
1970	1,115,653,000	1,110,924,000	1,223,011,000	1,167,418,194
1971	1,137,491,000	1,220,565,000	1,281,129,000	1,247,842,000
1972	1,377,034,000	1,468,706,000	1,631,419,000	1,530,842,500
1973	1,541,477,000	1,768,229,000	1,939,441,000	1,769,829,000 1/
1974	1,570,258,000	1,781,140,000	1,921,045,000	1,776,331,000 2/
1975	1,829,716,000	1,787,440,000 3/	2,188,250,000	2,085,579,000
1976	1,801,885,000	2,057,322,000 4/	2,225,648,000 4/	2,248,069,000 5/
Items Not Considered	---	123,646,000	123,646,000	---
1977	2,139,647,000			

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.

3/ Excludes contracts not considered by House due to lack of authorization.

4/ Excludes fellowships and training grants--not considered due to pending legislation.

5/ Appropriation Authority based on 1976 Conferees Allowance including training programs.

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1967	$931,753,000	$965,975,000	$1,000,975,000	$995,975,000
1968	1,069,072,000	1,065,746,000	1,114,187,000	1,065,746,000
1969	1,118,149,000	1,089,463,000	1,135,456,000	1,109,753,500
1970	1,083,420,000	1,084,626,000	1,195,215,000	1,141,485,000
1971	1,118,584,000	1,192,386,000	1,252,950,000	1,212,847,000
1972	1,316,308,000	1,404,989,000	1,565,919,000	1,502,591,000
1973	1,611,280,000	1,754,065,000	1,932,315,000	1,754,065,000 1/
1974	1,568,770,000	1,779,142,000	1,919,902,000	1,782,425,000 2/
1975	1,836,784,000	1,784,328,000 3/	2,195,350,000	2,089,897,000
1976	1,802,000,000	2,057,755,000 4/	2,226,081,000	2,248,126,000 5/
Items Not Considered	---	123,646,000	123,646,000	---
1977	2,139,647,000			

1/ No enacted appropriation. Authority was the Continuing Resolution.

2/ Appropriation after reduction.

3/ Excludes $246,293,000 contracts not considered by House pending legislative authorization. Library: $6,282,000.

4/ Excludes $123,646,000 NRSA training programs not considered by House pending legislative authorization.

5/ Based on 1976 Conferees Allowance plus unauthorized training programs, and including OD pay raise supplemental ($474,000).

Significant Items in House and Senate Appropriations Committee Reports

Item	Action to be Taken
1976 Senate Report	
1. The Committee suggested that NIH review its existing and prospective building plans and report on (a) substantive changes, (b) revised costs, and (c) relative priorities. (p.34)	The plans are being reviewed and a report will be ready by the time of the Congressional hearings.
2. The Committee requested a report on the number of grants and contracts over five years old and what is being done to review and evaluate them. (p. 36)	The report is in preparation - NIH's Division of Research Grants is collecting data - and the report is expected to be completed in March 1976.

Mr. FLOOD. Thank you very much.

WEDNESDAY, FEBRUARY 25, 1976.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. FRANK J. RAUSCHER, JR., DIRECTOR, NATIONAL CANCER INSTITUTE
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. GUY R. NEWELL, DEPUTY DIRECTOR, NATIONAL CANCER INSTITUTE
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
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. FLOOD. Now we have the National Institutes of Health, the National Cancer Institute. The presentation will be made by Dr. Frank J. Rauscher, the Director. We have a biographical sketch of you, Doctor, which we will place in the record at this point.

[Dr. Rauscher's biographical sketch follows:]

BIOGRAPHICAL SKETCH

Name: 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.

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. Distinguished Service Award—Presented by the Department of Health, Education, and Welfare. April 1975. Man of Science Award—presented by the ARCS Foundation, Inc. (Achievements Rewards for College Scientists), June 1975. American Cancer Society Annual Award, November 1975. And 59 publications on virology, cancer research, cancer planning and biomedical management.

Mr. FLOOD. You have some people with you, I see.

Dr. RAUSCHER. I have with me Mr. Earle Browning, our Financial Manager; Dr. Guy Newell, our Deputy Director; and Mr. Calvin Baldwin, our Executive Officer, and I believe you know these gentlemen as well.

Mr. FLOOD. I see you have a prepared statement, Doctor. How do you want to handle it?

Dr. RAUSCHER. It is a rather long statement, and I prefer to paraphrase some of the highlights.

STATEMENT OF THE DIRECTOR

Mr. FLOOD. Without objection, we will insert the statement in the record and you may comment briefly on it.

[Dr. Rauscher's complete statement follows:]

Mr. Chairman, and members of the Committee: We appreciate your confidence in the progress of the national effort to reduce the impact of cancer. We are mindful that the National Cancer program is the principal instrument for action against cancer for the benefit of all the people.

We have recognized the necessity, and indeed our responsibility under the law, to encourage active participation of scientists, health professionals, and public groups. A high priority has been given to improving coordination within the National Cancer program.

Mr. Chairman, our coordination activities have been an essential element in the progress of our research and control activities of the past year. They have helped to strengthen the relationships between the National Cancer Institute and the other components of the National Cancer program. These activities have also helped us to move more confidently toward our long-term goal of eliminating cancer as a major cause of death.

The proposed budget for fiscal year 1977 is before you. The accompanying budget justifications discuss the research and control activities of the National

Cancer program during fiscal year 1976, and the followup and new activities planned for 1977. At this time, I shall present some of the progress highlights of our research, control, and coordination activities.

ENVIRONMENTAL CARCINOGENESIS

It is now a universal opinion of scientists that cancer can, in the main, be attributed to environmental factors, and is largely a preventable disease. Those of us in cancer research and public health are aware that vigorous action is necessary to identify and control environmental cancer-causing agents, particularly among the thousands of chemicals that are in the environment in which we live and work.

A well-known example, and a large contributor to the environmental carcinogenesis problem, is cigarette smoking, the major cause of lung cancer. A few chemicals, such as arsenic and asbestos, are also well known occupational cancer-causing agents.

The approaches to identification, a prerequisite to elimination or neutralization of cancer-causing agents, must be indirect. We cannot test suspect carcinogens in people. The proof that a substance is a carcinogen must be accumulated from tests in animals and other laboratory systems, examination of cancerous tissue from patients known to have been exposed, and field studies relating suspect substances to cancer in people.

We are currently testing about 500 chemicals in laboratory animals. The compounds are selected on the basis of level of human exposure, the chemical structure, and preliminary information of their biological activity.

Much effort is going into development of short-term test systems, such as the use of cultured cells and microorganisms. The demonstration that a chemical causes mutations in such systems could be a warning of its possible cancer-causing activity and the need for comprehensive long-term testing in laboratory animals.

A major product of the field studies program was publication of an atlas showing detailed geographic variations in cancer deaths for 35 sites during 1950–1969. High cancer death rates were found in industrial counties, such as those concerned with production of chemicals, lumber, paper, and certain types of heavy machinery. These findings sparked much interest and numerous inquiries from communities throughout the country anxious to identify their cancer-causing problems. Other correlations suggested the effect of an environmental factor, possibly diet, in the above-average death rates for cancer of the colon and rectum in certain geographic locations.

In other activities, Cancer Institute staff have been involved in evaluation of specific substances. One was fluoridated drinking water. Medical and public health concerns about fluoridation of drinking water stimulated a Cancer Institute analysis of pertinent data. No evidence was found linking cancer to natural or artificial fluoridation of public water supplies. Cancer death rates in counties exposed to fluoridated water were not excessively high.

As a result of NCI advice based on our best scientific judgment, the EPA suspended the use of the pesticides aldrin and dieldrin, and the Occupational Safety and Health Administration (OSHA) of the Department of Labor decided to require a standard of exposure to vinyl chloride at the lowest level that technology can currently achieve.

A temporary Committee for the Review of the Data on Carcinogenicity of Cyclamate, appointed at the request of the FDA, has tentatively concluded that scientific evidence for the carcinogenicity of cyclamate has not been established. On the basis of recommendations that we shall make to the FDA, after the committee has given us its final report, the FDA will make a decision regarding approval for the marketing of cyclamate.

NCI staff also collaborated with other agencies and groups in joint problem-solving and cost-sharing projects, such as a jointly supported project with the National Institute of Environmental Health Sciences on developing information on testing systems for carcinogenesis. Extensive consultation and scientific documentation were provided to other Government agencies, such as the Food and Drug Administration, Environmental Protection Agency, and the National Institute for Occupational Safety and Health (NIOSH).

With its emphasis on systematic advancement of the knowledge of cancer-causing factors, the cancer control program has begun to implement an occupational cancer and information alert program through an interagency agree-

ment with OSHA and NIOSH. Through this mechanism, information and training about cancer will be made available to the workers of the country. The Cancer Institute is also supporting specific projects directed to a group of workers in asbestos and another group in vinyl chloride to provide medical surveillance and health education to the workers and their families to assure early detection of precancerous lesions and early cancer.

DETECTION AND TREATMENT OF CANCER

The impetus for advances in the research and control programs aimed at detection, treatment, continuing care and rehabilitation has continued. We can say with confidence that major new opportunities exist for significant improvement of survival of cancer patients.

In breast cancer as in all cancer, detection before the cancer has spread beyond the original site is crucial to increased survival. In the nationwide breast cancer detection demonstration projects we are sponsoring jointly with the American Cancer Society, the good results reported last year have continued. Some 80 percent of confirmed cancers had no regional node involvement, compared with 45 to 50 percent in the usual medical practice. About 40 percent of the cancers were detected by mammography alone. We expect to observe an improved rate of effective treatment following detection with the combined use of clinical history, clinical examination, mammography (xeroradiography), and thermography in these projects.

At the present time cancer is, in a large majority of cases, a systemic disease at the time of diagnosis. Clearly, then, the use of combined regional and systemic treatment when the disease is diagnosed and risk of recurrence is high, appears to be the key approach in treatment research.

Two major studies have shown that chemotherapy after mastectomy significantly lowers the recurrence rate in women with breast cancer whose axillary lymph nodes show evidence of cancer. One of the studies used the drug L–PAM as a postoperative treatment; the other used a three-drug combination of cyclophosphamide, metrotrexate, and 5-fluorouracil (CMF). The second study has led to an even more dramatic drop in the recurrence rate of breast cancer than did L–PAM. It is important to note that these are controlled studies with a significant number of patients—300 to 400—in each. Studies will continue through the use of new regimens and the addition of immunotherapy.

In the cancer control area, the Cancer Institute is supporting demonstration projects involving networks of cooperating community physicians and hospitals linked to major hospitals to disseminate the latest information and techniques in the diagnosis, treatment, and rehabilitation of breast cancer. The breast cancer networks involve development of about a dozen projects in as many States from New England to California.

In treatment of other types of cancer. progress has been made in the drug treatment of advanced cancers of the colon-rectum and stomach. These results have suggested the use of drug combinations as adjuvants to initial surgery for these types of cancer. Similar approaches will be pursued in all the major tumor types. Particular emphasis will be placed on ovarian cancer, in which patients with advanced disease have responded to new chemotherapy regimens. The addition of immunotherapy to chemotherapy in patients with acute myelogenous leukemia has led to an increase in the number of patients alive and free of leukemia, as compared with the number treated with drugs alone.

More effective treatment research is expected to result from a reorientation of the clinical cooperative group program, which has until now conducted clinical trials primarily of drugs. This program, consisting of 23 groups, is being expanded to emphasize combined modality research, including surgical oncology, radiation oncology, chemotherapy, and immunotherapy. In 1975, these groups involved 21,000 patients, and influenced the treatment of 10 additional patients for every patient in the clinical trials.

Four anticancer drugs have now been approved for general medical practice and are in use. The drugs are: Adriamycin, which has wide usefulness against a broad range of tumors, including cancers of the bone and soft tissue. DTIC, for treatment of advanced malignant melanoma; and CCNU and BCNU, members of a new chemical class of anticancer drugs. The latter two drugs can penetrate the so-called blood-brain barrier, and therefore are useful in treatment of primary and metastatic brain tumors.

In attempts to improve early detection of cancer in people, some cancer control efforts are directed to individuals at high risk to cancer. Some 35 States are cooperating in the uterine cervical cancer screening program dealing with women at high risk who have not previously had the Pap test. By the end of fiscal year 1977, an estimated 3.5 million screenings will have been performed. Early stages of cancer and abnormal changes in the cervix may be identified with the Pap test 5 to 10 years before symptoms of cancer appear, allowing opportunity for curative treatment.

Another activity in followup of special population groups concerns before-birth exposure to diethylstilbestrol (DES). We are supporting four institutions in a cooperative study of about 4,000 young women born between 1943 and 1963 to mothers who received DES or other synthetic estrogens to prevent abortions during pregnancy. The young women will be followed for 5 years or more for cancer and other abnormalities of the genital tract. The detection and diagnostic procedures developed in this study may then be applied to the larger population at risk.

A new diagnostic technique, computer-assisted X-ray tomography, has revolutionized the diagnosis of brain tumors and other brain diseases. It is a technique for making a series of thin cross-section radiographs of brain tissue. It permits location of tumors in a way not previously observable by X-ray. Active development is underway to adapt the machine to make cross-section images of cancer sites in other parts of the body.

COMMUNITY OUTREACH PROGRAMS

The National Cancer Institute is supporting a new program in which projects will be developed in a few communities to demonstrate the full range of cancer control techniques, from prevention through continuing care and rehabilitation. The goal is to determine the impact of coordinated cancer control efforts on the cancer problem in those communities.

Each community will select for demonstration three to five types of cancer, such as breast, uterine cervix, and lung. The communities will each organize a coordinated effort including public medical schools, cancer centers, private physicians, voluntary groups such as the American Cancer Society, and State and local health departments. The communities must have in operation a population-based cancer data system. The Cancer Institute will provide partial support to a maximum of 5 years, at which time the programs will be expected to become self-supporting within the communities.

Nine planning contracts have been awarded. Negotiations are in progress with two communities for implementation contracts.

Another community activity has been the establishment of a communication network through the 17 comprehensive cancer centers. This network will provide a major means for the Cancer Institute and the centers to provide cancer information to health professionals, cancer patients, and those at risk to cancer. Toll-free telephone service and resources for cancer information are being established at the centers. The American Cancer Society, National Cancer Institute, and centers have been working together to assure that this program will be conducted in a cooperative way, and with the support and involvement of other cancer-related and community organizations.

BASIC RESEARCH

The foundation for the national cancer program is basic research. Information from basic biomedical research supported by the Cancer Institute increases the total accrued knowledge. Most importantly, research in cancer biology provides a basis for attacking problems of diagnosis, treatment, and prevention of cancer. The best course to follow at present is to invest about half our funds in basic research.

The role of viruses continues to be studied with the objective of learning more about causation of cancer and ways of preventing it. Viruses under study include a virus isolated from the laboratory-grown leukemic cells of a patient with acute myelogenous leukemia, a rare form of blood cancer; a virus isolated from laboratory-grown human embryo cells; and a virus isolated from the brain tumor of a patient with an inherited immunologic disorder.

Scientists have pinpointed the location of a virus gene that is responsible for the cancerous transformation of infected animal cells. This information indicates that it may be possible to separate the cancer gene from the other genes of the

virus. Isolation of the viral cancer gene would simplify efforts to understand how normal cells become converted to malignant cells. Other basic research is devoted to the structure and behavior of cells, the chemical molecules and processes within cells, and the immune system of people.

COORDINATION A HIGH PRIORITY

Extensive efforts are in progress to involve within the national cancer program all groups, both NCI-supported and non-NCI supported, concerned with cancer. Non-NCI-supported organizations represent a significant portion of the national cancer research and control efforts. They include other NIH institutes, other Federal agencies, State and local governments, institutions such as hospitals and universities, voluntary groups such as the American Cancer Society, professional groups, and industry. The efforts of non-NCI-supported groups are coordinated within the cancer program through voluntary actions, such as participation in joint meetings and memberships on committees dealing with various problem areas.

Coordination for NCI-supported groups is carried out through the 17 comprehensive cancer centers, specialized centers, organ-site projects and task forces, the clinical cooperative groups, international activities, and interagency coordinating committees. Support is also given through consortium grants and contracts, interagency agreements, and conferences, symposia, and workshops.

The purposes of coordination are information exchange to avoid undesirable overlap and duplication, and to identify areas of action appropriate to the various components in the cancer research and demonstration efforts across the country.

The new 18-member Federal Interagency Coordinating Committee for the national cancer program had its first formal meeting recently; the Interagency Collaborative Group on Environmental Carcinogenesis, representing 20 Federal agencies and subagencies, continues to meet regularly for exchange of information and identification of areas of action; and an interagency coordinating committee for cancer control and rehabilitation has been established.

In the international program, the international cancer research data bank program has made further good progress in coordinating the exchange of cancer information. Cancerline, the computer-based cancer information system, links the computer system at the National Library of Medicine in Bethesda with terminals in more than 500 locations in the United States and in several countries throughout the world.

The Cancer Institute has numerous liaison and collaborative activities ongoing with international cancer research organizations. It has formal agreements for collaboration with the governments of the U.S.S.R., Japan, and Poland, and is planning collaborative activities with other countries—France, the Federal Republic of Germany, the Republic of China, and Egypt—in the interests of furthering our cooperation with these countries. On a scientist-to-scientist basis, joint research projects are in progress in the United States and many other countries around the world.

In a new activity, we have taken the initial steps to develop a national cancer program informaiton clearinghouse, which will serve as a reference center for cancer information available from and for all components of the national cancer program.

CONCLUSION

In the past years, our primary emphasis has been in detection and treatment, to make every effort to help people afflicted with cancer. We think we shall be able to make an impact on some of the major cancers. A number of years will have to elapse before we can be sure that the new directions in detection and treatment are affecting national survival figures. Recent statistics, however, have shown an encouraging trend. Overall, for women up to age 55, the chances of dying of cancer have perceptibly decreased in the period 1968 to 1974, and the same trend is true for men up to age 45.

Now, the time is right to give emphasis to environmental carcinogenesis and the potential this area carries for prevention. We have made progress in understanding the causes of about half of environmental cancers—that is, those due to smoking and to occupational exposures in men. We must learn how to prevent those cancers whose causes we know, and to identify the causal factors for the others. The new diet, nutrition, and cancer program is getting underway in this area.

Mr. Chairman, we believe that the advances to date in research and control activities and the effectiveness of coordination of the national cancer program will contribute significantly to its success and the ultimate control of cancer. I would like to insert into the record a listing of more than 60 accomplishments of the national cancer program.

APPROPRIATION REQUEST

Mr. Chairman, the request for the National Cancer Institute totals $687,670,000. The new request includes: $181,572,000 for "Cause and prevention research"; $44,390,000 for "Detection and diagnosis research"; $221,229,000 for "Treatment research"; "$116,071.000 for "Cancer biology"; $32,310.000 for "Cancer centers support"; $27,758,000 for "Research manpower development"; $10,907,000 for "Construction"; and $53,433,000 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.

Dr. RAUSCHER. Thank you.

Mr. Chairman, since the first Cancer Act of 1937, my predecessors, as Director, and many other people from the private sector have come to committees of the Congress primarily to describe research findings and to try to explain what that promise for the future might mean.

Today I would like to tell you what we have actually done for people, primarily since the Cancer Act of 1971, as renewed in 1974. Some of these accomplishments are due to things started since that time. Others are an accrual of projects started before that time. But in effect what I tried to do is to determine just what has been done that has actually resulted in the saving of lives primarily through treatment and the prevention of cancer as well. It is these points that I would like to discuss very briefly this morning.

If I may also, Mr. Chairman, I would like to insert some 60 points of direct people benefit for the record as an addendum to my statement.

Mr. FLOOD. Without objection, that will be done.

[The information follows:]

NATIONAL CANCER PROGRAM

NATIONAL CANCER INSTITUTE

ACCOMPLISHMENTS OF BENEFIT TO PEOPLE SINCE 1971

Since enactment of the first National Cancer Act in 1937, Directors of the National Cancer Institute and many others, including the American Cancer Society and others of the private sector, have testified at hearings of the Congress primarily in terms of research finding and their promise for the future. This was necessary, and predictable, because of the complex nature of this chronic disease, which occurs in more than 100 forms. Since that time, many studies have been conducted, and importantly, the Congress and executive branch gave renewed support to the Cancer Institute in 1971. Because of these activities and this support, we are now able to report new and accrued [1] accomplishments of direct and definitive benefit to patients through advances in diagnosis, treatment, and rehabilitation, and to prospective patients through advances in detection of risk and prevention. In every sense, these advances are remarkable and have already saved many lives. The accomplishments listed in the following pages also include the traditional milestones of research progress, many of which with time, and public patience and support, will reduce and eliminate the diseases we call cancer.

ACCOMPLISHMENTS OF DIRECT BENEFIT TO PEOPLE

A new treatment strategy of giving anticancer drugs postoperatively to women with breast cancer and a high risk of recurrence has significantly lowered the

[1] Including projects started before 1971, but which have "borne fruit" since 1971.

recurrence rate among such patients. One breast cancer study used the drug, L–PAM, as a postoperative treatment: another used a three-drug combination called CMF. The second study led to an even more dramatic drop (5 times better than that prior to 1971) in the recurrence rate than did L–PAM. There is great and justifiable cause for optimism in these results, because experience has shown that prolonged tumor-free survival leads to increased survival rates. About 90,000 women develop breast cancer each year in this country alone. And about 33,000 will die with this disease this year. Breast cancer kills more American women than any other disease at peak ages of risk and therefore often at prime ages of their lives. These dramatic results can only mean that many American women, who would have died, will live virtually normal lives and normal life expectancies.

A study of the treatment of breast cancer with less radical surgery has shown to date that it may be as effective as radical surgery. If the trend continues, the results will lead to treatment tailored to the individual patient and in many cases significanly different from the traditional radical surgery.

With the use of postoperative drug treatment with either high doses of methotrexate followed by an antidote (citrovorum factor) or Adriamycin, a new drug, the 2-year survival rate for osteogenic sarcoma has been increased from 20 to 80 percent. Osteogenic sarcoma, a tumor of the bone, occurs most often in young people.

More than 50 percent of children with acute childhood leukemia treated at various centers in the Nation now survive more than 5 years without disease. In 1972, I reported that in the best of institutions and under the best of circumstances over 90 percent of children with this disease could be put into remission and that about 50 percent were alive a full 5 years after diagnosis. In 1972, only about 25 percent of American children had access to this kind of treatment. I am pleased to report that now at least 75 percent of our children are getting this kind of diagnosis, referral, and treatment. Even this accessibility will be improved, not only for acute lymphocytic leukemia, but for other childhood cancers as well.

The addition of immunotherapy to chemotherapy in patients with acute myelogenous leukemia has led to an increase in the number of patients alive and free of leukemia, as compared with the number treated with drugs alone. In immunotherapy, agents are used to stimulate the immune defense system of the patient.

With the treatments now available at certain centers, more than 90 percent of patients with early Hodgkin's disease, and about 70 percent with advanced disease, are surviving 5 years. Many of these are free of disease and are expected to live normal lifetimes. Recent update of these data show that those achieving a complete remission with drugs have a 66 percent chance of remaining free of disease up to 10 years.

Some patients with various types of advanced non-Hodgkin's lymphomas can be cured (have up to 9 years without evidence of disease) by use of drug combinations. The application of these combinations to patients with early disease in conjunction with radioterapy is being studied.

It is firmly established that chemotherapy (drug treatment) combined with surgery and radiotherapy is curative in 80 to 90 percent of patients with Wilms' tumor, a previously fatal childhood cancer of the kidney.

The use of drugs and X-ray therapy in treatment of Ewing's sarcoma, another type of cancer that afflicts children, has led to markedly improved survival of patients with this disease.

Significant progress has been reported in the treatment of advanced malignant melanoma, a relatively rare form of skin cancer, by chemoimmunotherapy, a combination of an anticancer drug (DTIC) and a killed bacterial vaccine (BCG), which stimulates the immune defense system of the patient.

The first successful combination drug treatments of advanced cancers of the colon-rectum and stomach have been reported. Trials of these drug combinations immediately after surgery to increase the cure rates after the primary treatment are now in progress. If this therapy is as successful as it appears, it could significantly reduce the 49,000 annual deaths due to cancer of the large intestine.

Important developments in the supportive care of cancer patients include transfusions of blood components, such as platelets to prevent hemorrhage and white blood cells to treat infections; and laminar flow rooms to provide an environment that protects patients against infections.

A test that predicts the response of patients with recurrent breast cancer to treatment with hormones has been developed and is in clinical trial. Presence of a protein (estrogen receptor protein) in the tumor predicts a positive response

to removal of hormone sources (ovaries, adrenals, or pituitary gland). Between 40 and 50 percent of breast cancers have cells containing the receptors. Absence of the protein, indicating that there would be no response to hormone treatment, will spare a patient a useless operation. Such patients can instead be given therapy with anticancer drugs.

CCNU and BCNU are members of a new chemical class of anticancer drugs now being developed, and will soon be available for general medical practice. These drugs can penetrate the so-called "blood-brain barrier," and are therefore very important in the treatment of primary and metastatic brain tumors.

Adriamycin, a new anticancer drug, was approved as a prescription drug by the Food and Drug Administration in 1974 for use in cancer patients. Adriamycin has activity against a broad range of tumors, including cancers of the bone and soft tissue.

DTIC, a new anticancer drug discovered and developed by the National Cancer Institute, became available as a prescription drug in 1975. It has activity against malignant melanoma.

Maytansine, a plant product recently discovered by scientists in the National Cancer Institute drug development program, has high activity against leukemia in laboratory animals. Preliminary clinical trials have been started against this and other cancers.

Seventeen Comprehensive Cancer and many other specialized centers located around the country are a national resource for basic research, clinical research, community involvement, continuing education of health professionals, research training and communication of cancer information. Patients are 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.

A communication network has been developed through the 17 Comprehensive Cancer Centers to provide cancer information to health professionals, cancer patients, and those at risk to cancer. Toll-free telephone service and resources for cancer information are being established at each Center.

The clinical cooperative group program, which has been in existence for some years to conduct clinical trials primarily of drugs, has been expanded to emphasize combined treatment research including surgical oncology, radiation oncology, chemotherapy, and immunotherapy. In 1975, the 23 groups in the program involved 21,000 patients, and influenced the treatment of at least 210,000 additional patients.

The cancer control program is supporting demonstration projects involving networks of cooperating community physicians and hospitals linked to major hospitals to disseminate the latest information and techniques in the diagnosis, treatment, and rehabilitation of breast cancer (12 networks); head and neck cancer (10 networks); and childhood leukemia and lymphoma (7 networks).

The International Cancer Research Data Bank Program (ICRDB) is actively promoting worldwide exchange of information among cancer scientists. The ICRDB Program is operating an online computer information retrieval system called Cancerline (Cancer Information on-Line). It links the computer system at the National Library of Medicine in Bethesda with terminals in more than 500 locations in the United States and in several countries throughout the world. Cancerline presently contains more than 45,000 abstracts of worldwide published papers dealing with cancer therapy and carcinogenesis. Information on more than 9,000 ongoing cancer research projects and clinical cancer therapy protocols are being processed and added to the data base for online use by research investigators and clinicians worldwide. This is in direct compliance with directives from the Congress in 1971 and 1974.

A nationwide breast cancer detection demonstration program cosponsored with the American Cancer Society, encompassing 27 projects is underway in 25 States. Some 230,000 women have been examined and 4,000 biopsies have been reported. Of these, about 800 have been determined to be cancer. About 77 percent of confirmed cancers had not spread, a condition crucial to increased survival; this compares well to the 45–50 percent of patients diagnosed with localized cancer in the usual medical practice. About 40 percent of the cancers were detected by the technique of mammography (X-ray) alone.

More than 30 States are cooperating through their health departments in a uterine cervical cancer screening program, giving the Pap test to women at high risk who have not previously had it. By the end of fiscal year 1977, an estimated 3.5 million screenings will have been performed. Not only early stages of cancer,

but abnormal changes in the cervix may be identified 5 to 10 years before symptoms of cancer appear, allowing major opportunity for curative treatment.

A prototype cell-sorting machine has been able to analyze cervical cytology specimens and identify more than 90 percent of the abnormal specimens. This is a significant step toward the goal of automation of the reading of Pap test specimens. The number of technicians and laboratories presently available is inadequate to conduct the number of tests required with the existing technique. The cell-sorting machines under development are designed to scan specimens rapidly and select those with abnormal cells for subsequent analysis by trained personnel.

Use of an improved fiberoptic endoscope, a flexible instrument that permits determination of the location and extent of the tumor, is assisting the detection of cancer of the colon in earlier stages. The instrument is also proving valuable in the diagnosis of cancer of the pancreas.

Six radiological physics centers were established to assist medical physics practice in cancer diagnosis and treatment, such as standardization of quantity and extent of radiation given. This important quality control mechanism has served as a model for the benefit of the millions of Americans undergoing diagnostic radiologic procedures yearly, and the more than 400,000 cancer patients receiving radiation therapy yearly.

Computer-assisted X-ray tomography is a new technique that has revolutionized the diagnosis of brain tumors and other brain diseases. It is a technique for making a series of cross-section radiographs of brain tissues. It permits location of tumors in a way not previously observable by X-ray. Active development is underway to adapt the machine to make cross-section images of cancer sites in other parts of the body.

A large study featuring cell examination of sputum and chest X-rays to detect lung cancer in heavy smokers without symptoms of the disease has screened approximatey 20,000 individuals and found some 150 cancers. The study has already shown that early lung cancer can be detected in this way and that the fiberoptic bronchoscope can diagnose the exact location and extent of the tumor for surgical treatment. Many of the tumors were small enough that survival is expected to be better than usual in patients with lung cancer.

A cancer control project is supporting observation of at least 4,000 young women, born between 1943 and 1963, who were exposed before birth to a drug, DES, which their mothers received to prevent abortions during pregnancy. The young women will be followed for 5 years or more for cancer and other abnormalities of the genital tract. The detection and diagnostic procedures developed in this study may then be applied to the larger population at risk.

New chemicals found to be carcinogenic include vinyl chloride, chlordane, trichloroethylene, ethylene dibromide, heptachlor, DES, and Kepone.

New chemicals regulated include aldrin, dieldrin, vinyl chloride, and Red Dye No. 2.

Less hazardous cigarettes have been developed and evaluated in newly developed inhalation smoking machines. They are now on the market. Acceptance by the public will have a major beneficial impact on reducing the number of new lung and other cancers.

Progress has been made in developing relatively quick, inexpensive laboratory techniques for identifying potential cancer-causing chemicals for test in the laboratory animal test systems. We are evaluating one procedure in which test chemicals are injected into pregnant hamsters; the embryos are removed and their cells grown in laboratories. Evidence of cancerous transformation can be detected in as little as 2 weeks instead of the usual 3 or more years and at a cost of $1,000 instead of $100,000. In another test, the ability of a chemical to cause genetic mutation in bacteria in cultured cells could be a warning of its possible cancer-causing activity.

Tests are currently in progress on about 500 chemicals to determine their cancer-causing ability in laboratory animals. The compounds are selected on the basis of level of human exposure, the chemical structure, and preliminary information of their biological activity. Among the chemicals being tested are pharmaceuticals, industrial chemicals, pesticides and agricultural chemicals, metallic compounds, and in addition, natural materials, food additives, and a variety of other environmental chemicals and intermediates.

A series of monographs, "Evaluation of Carcinogenic Risk of Chemicals to Man," has been published by the International Agency for Research on Cancer with direct support and collaboration from the National Cancer Institute. These

volumes bring together the results of testing of many chemicals for their cancer-causing ability, provide a quick reference for investigators, and prevent unnecessary duplication of testing. Eight volumes have been published covering more than 200 substances for which there is a significant human exposure and some published evidence of carcinogenicity in animals and/or man. A ninth volume is in press.

Publication of an "Atlas of Cancer Mortality for U.S. Counties: 1950–1969" has pinpointed geographic concentrations of cancer throughout the country. High cancer death rates were found in industrial counties such as those concerned with production of chemicals and certain types of heavy machinery. These findings have led to numerous inquiries from communities throughout the country anxious to identify their cancer-causing problems, and they will continue to be analyzed by Institute scientists to identify high risk counties and groups of people. We shall identify environmental factors in the causation of cancer and important host/environment interactions.

A cancer control prevention project for workers in Tyler, Tex., exposed to asbestos and another one for workers in Louisville, Ky., exposed to vinyl cholride, both proved carcinogenic substances, provide medical surveillance and health education to the workers and their families to assure early detection of precancerous lesions and early cancer. Through programs such as these, models will be developed for monitoring high risk workers exposed to carcinogens and for identifying procedures that will provide early warning of an impending malignancy.

A statistical association was established between the amount of beef consumed in the diet and an increased occurrence of colon cancer. This information was obtained in a study of colon cancer among Hawaiian residents of Japanese descent. The risk of colon cancer for persons who no longer ate Japanese-style meals but had adopted Western-style meals was about twice that of persons whose diet had remained relatively unchanged. The findings in this study are not considered sufficient to label beef consumption as cancer causing but they assist in the planning of research in different population groups on the complex sequence of events leading to colon cancer.

The new SEER program (surveillance, epidemiology, and end results reporting) is monitoring the trends in cancer incidence, changes in diagnostic and treatment priorities, and associated survival rates of cancer patients. This program will provide continually updated information on cancer statistics in the United States and will therefore serve as a direct check on how well (or how badly) we are doing.

A new report has been published on trends in survival rates of patients with cancer. One-year survival results for patients with diagnoses made during 1970–71 suggests that improvement in the 5-year survival observed during the 1960's for many forms of cancer will be sustained. Continued reporting of survival for patients treated in the 1970's is expected to demonstrate that recently introduced therapies have been increasingly effective.

The cancer control program is supporting projects in several communities to demonstrate cancer control techniques, from prevention through continuing care and rehabilitation, relating to a few types of cancer as selected by the communities. The goal is to determine the impact of coordinated cancer control efforts on the cancer problem in those communities.

The cancer control program is supporting the training of health professional groups to assist in continuing care and rehabilitation of cancer patients. These groups include an estimated 3,600 physical and occupational therapists, rehabilitation teams, maxillofacial prosthodontists, enterostomal therapists, and nurse oncologists.

Scientists within and outside the national cancer program have found again that fluoridation of drinking water does not contribute to a cancer burden for people. The fact, with existing information, that fluoridation of water does not cause cancer in people has also been confirmed and reiterated by the Royal College of Physicians of the United Kingdom. This is also important because continued fluoridation of water will help curb what many have called the most prevalent disease of people—dental caries.

Accomplishments in Effective Management, Planning, and Coordination

A 5-year national cancer program plan, updated annually, provides a framework for coordinating, monitoring, updating, and reporting progress of the national cancer program. I am especially proud of this important endeavor by the scientific community and my staff. It is unique and is in direct compliance with congressional mandate.

An interagency coordinating committee for the national cancer program comprising 18 Federal agencies and operating groups assists the coordination of Federal cancer research and demonstration efforts across the country.

The interagency collaborative group on environmental carcinogenesis representing 20 Federal agencies and subagencies meets regularly for the purpose of exchanging information and identifying areas of action appropriate for inclusion under the national cancer program in areas of research, monitoring, surveillance, and epidemiological studies. Through this committee the National Cancer Institute has an opportunity to provide its scientific judgment to regulatory and other Government agencies for their use in such activities as setting standards for protection from environmental chemicals.

International collaboration in cancer as directed under the National Cancer Act includes formal agreements with the governments of the U.S.S.R., Japan, and Poland, and additional cooperative projects in more than 20 countries. Effective coordination and cooperation have been achieved with the World Health Organization, the International Union Against Cancer, and other international organizations concerned with cancer. The results of our international activities are expected to benefit the American people as well as peoples throughout the world.

ACCOMPLISHMENTS IN BASIC RESEARCH FOR FURTHER BENEFIT TO PEOPLE

Two studies specifically on the black population in the United States have been published. One study reported generally lower survival rates among black cancer patients as compared with white patients in the study, even when the disease was diagnosed at a localized stage. This study covered cancers diagnosed in black patients between 1955 and 1964 in selected hospitals. The difference between black and white patients was greatest among patients with bladder cancer and among female patients with cancer of the body of the uterus. However, for cancers of the kidney, survival was more favorable among black patients than among white patients. The other study on the occurrence of cancer showed high rates for black males for all sites combined, and low rates for black females. These studies are an important step in the search to understand and improve our ability to control cancer in the black population.

Publication of the data from the Third National Cancer Survey presents information on all cancers newly diagnosed during the 3-year period 1969–71 in seven metropolitan areas, two entire States, and the Commonwealth of Puerto Rico. Among the important findings were indications of a significant increase in cancer among U.S. black males, particularly cancer of the prostate, esophagus, and lung, and a trend toward a more uniform incidence across the country. It was also found that skin cancer occurs much more often than previously estimated. Comparisons of these data with those obtained in previous surveys taken in 1939 and 1948 are being evaluated to pinpoint possible contributing factors in cancer occurrence. The Third National Cancer Survey Data were utilized in preparing the second edition of another publication, "Cancer Rates and Risks." This publication presents cancer information in the form of questions and answers with accompanying charts and tables.

A diet, nutrition, and cancer program is developing projects to produce and disseminate information on nutrition for cancer patients and on the relationship between nutrition and cancer causation. Efforts will be directed to assisting cancer patients in their nutrition problems.

Six organ-site programs are studying laboratory and clinical aspects of the cancers that strike most Americans—cancer of the breast, lung, large bowel, bladder, prostate, and pancreas. By coordinating research on detection, diagnosis, treatment, and prevention for these types of cancer, we hope to more quickly increase our ability to control the major cancer killers.

New leads have emerged in the treatment of ovarian cancer, the fifth most common cancer killer of women, opening the way to combination of surgery and postoperative drug treatment as in breast cancer.

In the continued search for new anticancer drugs, some 20 new agents were identified as having potential for further development in the past year.

A purified form of CEA, a "marker" protein found in the blood and called carcinoembryonic antigen, appears to be very specific for detecting cancer of the large bowel. CEA is being evaluated as a diagnostic test in patients with symptoms of the disease and as a screening test in persons without symptoms.

A virus from leukemic cells of a patient with acute myelogenous leukemia, a rare form of blood cancer occurring primarily in adults, has been isolated and found to be similar to the two viruses that cause cancer in nonhuman primates,

the gibbon ape and woolly monkey. This finding does not indicate that leukemias, or other cancers, are contagious in man either by coughing, sneezing, or any other forms of contact with cancer patients. 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 may also 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.

New knowledge has been obtained of the internal component parts of RNA viruses, of which the virus from the leukemia patient is a member. RNA viruses are known to cause many kinds of cancer in a wide variety of animals, including rodents, chickens, cats, and subhuman primates. Such studies are expected to lead to a better understanding of how a virus may insert some part of itself into the genes (biologic units of heredity) of a cell, thus causing a permanent change in the cell's growth pattern, which may in some cases lead to development of cancer. With this understanding, ways of blocking the viral action could be studied.

Evidence has been obtained to show that only a small part of the genetic material of a cancer virus controls tumor induction. This information indicates that the chances are good for separating the cancer gene from other genes of the virus. Isolation of the viral cancer gene would simplify efforts to understand the transformation of normal cells into tumor cells.

A recent finding of potential importance for the prevention of cancers in man is the protection of laboratory animals against cancer, using vaccines prepared against viruses isolated from certain chemically induced tumors. Pure chemicals such as the well known contaminant of our envrionment, DMBA, induce cancers in animals. Viruses isolated from these chemically induced tumors were used for the preparation of the vaccines. Cancers developed far less frequently, or much later than expected, in other animals treated with these vaccines before exposure to DMBA and related carcinogenic chemicals. This could mean that a virus (or a piece of it "picked up" by a "normal cell") is responsible for many human cancers as a result of activation by chemicals; and that at some future time, we may be able to live in a contaminated environment and not develop cancer, if we are protected by a vaccine or some other factor that prohibits chemical activation of viruses that we may have carried within us from birth.

A human DNA virus was isolated from the brain tumor of a patient with a hereditary disorder called Wiskott-Aldrich syndrome. Patients with this disease have immunologic defects and a high cancer rate. Detailed studies of the virus and other patients with Wiskott-Aldrich syndrome suggest that the virus caused the tumor.

Differences between the membranes of normal and malignant cells are under study because scientists believe that tumor-inducing activity of cells is determined by their cell surface properties. Scientists comparing cancer and normal cell membranes have found differences in the way they line up together, immunologic activity, clumping with certain chemicals that act as a glue, and amounts of chemical components. This is important because cancer starts in a cell or a group of cells. Malignant cells have altered surface properties that may account for such basic characteristics of malignancy as invasion of normal cells and disorganization of the growth pattern. Studies of the properties of malignant cell membranes help us to understand how normal cells lose their growth controls, so that preventive action will be possible.

In immunology, one of the most important fields in basic cancer research today, new information about the role of white blood cells) part of the immune defense system) was obtained in a study of patients with a rare disease of the immune system called CVH. In some patients, CVH precedes the development of cancer. This is important because we need to understand the nature of the defect in a cancer patient's immune system, with the result that it fails to "recognize" cancer cells as "foreign invaders."

A system has been developed for ranking thousands of chemicals for their estimated risk for carcinogenic potential. This information will help use the bioassay test resources most efficiently, and will also provide early guidelines to the chemical industry as to the potential hazard of a new chemical compound about to be introduced into the environment.

The Frederick Cancer Research Center was established at Fort Detrick, Md., to conduct viral oncology research, chemical carcinogenesis research, and basic research in support of the national cancer program. It has already become one of the Nation's best oncology laboratories.

A new clinical cancer education program supports the improvement of cancer education in colleges and universities at the undergraduate and graduate levels, and promotes continuing cancer education of physicians, dentists, and other health professionals in schcools of medicine, dentistry, and public health, in major hospitals affiliated with medical schools, and in specialized cancer institutions.

BREAST CANCER

Dr. RAUSCHER. Thank you very much. The first point I would like to speak to is the dramatic improvement in our ability to treat women with breast cancer. This is what we call adjuvant chemotherapy or the treatment, as you know, with drugs following surgery. We have effected at least a five-fold improvement in the number of women surviving without any recurrence of their cancer. This has been accomplished primarily since this program started in 1971. I make this my first point, Mr. Chairman, because as many as 90,000 American women develop breast cancer each year and 33,000 die. It is by far the principal cancer killer of women, many of whom are at the prime of their lives. This is the major cancer in women. So we are very excited about this technology not only for the benefit to American women and women throughout the world where this technology is now being used, but also due to our belief that we can translate this into the treatment of other major cancer; specifically cancer of the large bowel in man which in the American male is the second killer due to cancer.

LEUKEMIA

Now I could say much the same thing about the dramatic—and I believe that is the word—improvements in our ability to treat acute lymphocytic leukemia in children. When I first testified some years ago, I said we thought we were developing means to put about 95 percent of such children into remission, and it looked as though we were going to have a high percentage of long-term survivors. I can now report to you that about 55 percent of children so treated are alive and without apparent disease 5 years after diagnosis and treatment with various combinations of drugs.

Three years ago, I mentioned also that although we were having success in this area, I was very concerned with the fact that only about 20 percent of the children in the country had access to the expertise required. I can now assure you that about 75 percent of such children have access to this kind of very effective treatment for acute leukemia. The same thing can be said of bone tumors, melanoma, and Hodgkin's disease. Some 80 to 85 percent of people with Hodgkin's disease are now alive 5 years and many 15 years after the diagnosis. This was unheard of 5 or 10 years ago.

Within the past year and a half we have effected a dramatic improvement in our ability to keep children alive with osteogenic sarcoma, a bone cancer, beyond 2 years, again many of these are without apparent disease at this time. Whereas before, 80 percent of these children would have had recurrences and died. Now less than 10 percent get recurrent disease within 2 years. Many physicians in the country are using the frank word cure, and this, as you well know, was not used just a few years ago. There are many other examples I could give you of our improvement in cancer treatment and patient survival.

This past year we have also seen a marked improvement in the sur-

vival of men, in particular with cancer of the large bowel. This, as I mentioned before, is the second most prevalent killer in American men from cancer.

We confirmed recently a test which can determine whether a breast cancer has what we call estrogen receptors. It is a chemical structure on the surface of their tumor cells. The tumors of about 50 percent of afflicted American women have this indicator substance. The reason this is important is if they have this receptor, then we know they can probably profit from hormone treatment. If they do not, we know already that this form of treatment will not serve that patient well. So it means in a very practical sense that we can avoid possibly unpleasant and unnecessary procedures in some cases for women who do not have this kind of receptor. Very importantly, it means we can predict which is the best form of treatment for an individual woman.

I mentioned last year to you and members of the committee that adriamycin was an exciting drug. It has the widest range of activity among different cancers of any drug we know. Our colleagues at the Food and Drug Administration have approved the use of this drug by the practicing physicians, and it is now being used either alone or in combination against a broad range of tumors throughout this country.

COMPREHENSIVE CANCER CENTERS

Much of what I am talking about has been made possible through what we call our comprehensive cancer centers. I know you and others have been concerned about how we have been setting up networks around the country, based on the community physician in the community hospital, either alone or tied in with the expertise of a comprehensive center. Seventeen comprehensive centers have already been established and are now fully operational. About 106 million Americans live within 120 miles of a center. This, in a practical sense, means that many can be seen on an outpatient basis and are not drawn away from their families for any length of time. Because of their illness, that closeness, we feel, is very important so as not to overtax their strength.

CLINICAL COOPERATIVE GROUPS

We have expanded what we call our clinical cooperative group program. These are groups of physicians all over the United States that are banding together to share patient information and to use common protocols for drugs, common surgery and radiation therapy programs. This past year alone 23 cooperative groups have directly involved 21,000 patients and have influenced the treatment of an additional 210,000 cancer patients in the United States. We feel that these groups are at the forefront of knowing what is best for the individual patient. More and more, through our coordination, they are beginning to tailor the forms of treatment for the individual patient by combining surgery, radiation, chemotherapy, and in some cases the new treatment called immunotherapy, which is designed to strengthen the body's natural resistance to cancer.

INFORMATION DISSEMINATION

In terms of information dissemination, the Congress some years ago said we should develop an International Cancer Research Data Bank.

This is now becoming fully operational and will include all of the major institutions throughout the Western World and to some extent in places like the Soviet Union and Japan.

We have well over 100,000 pieces of information, that is, abstracts of published papers in our computer. We call it the Cancerline. This is accessible to anyone having a very inexpensive telephone hookup capability. This has proven to be a very popular and effective way of telling people what is going on.

In this regard, also, we have many thousand notifications of different experiments ongoing. This is important because if I were an investigator in a laboratory in Pennsylvania, I would want to pick up the phone and call somebody and find out what I intended to undertake, to what extent that is already ongoing. So it is a means of avoiding unnecessary duplication.

BREAST CANCER DETECTION CENTERS

I mentioned last year also that we were well into the development of a national network of breast cancer detection centers. There are now 27 of these cosponsored with the American Cancer Society throughout the United States. Already some 230,000 women have been evaluated. We found 800 cancers essentially in nonsymptomatic women. Women who are alarmed and concerned about the high incidence of breast cancer in this country come in at no expense to them to determine whether a lump is present, they receive thermography and the latest in x-ray mammography to supplement regular physical examination.

It is heartening that about 77 percent of those women found to have cancer still have them localized to the breast; it has not yet spread beyond the breast. That is critically important because these women have a very good prognosis for a long and essentially normal life span.

CAUSE AND PREVENTION

In the area of cancer causation and prevention, within the last 4 years the NCI, together with other sister agencies, have determined a number of chemicals that affect people in the sense of their being carcinogenic. You know about vinyl chloride and pesticides such as chlordane; also, trichloroethylene, ethylene dibromide, heptachlor, diethylstilbestrol and Kepone, which has been in the news a great deal lately. All of these have been found to be carcinogenic through this and related programs.

In addition to that, by providing information to the regulatory agencies such compounds as dieldrin, vinyl chloride, aldrin and red dye No. 2 have been regulated. I think this can only mean that man's carcinogenic burden is decreasing.

We have 500 additional chemicals on test at the present time and within the next 12-month period some 203 compounds will be coming off, having been fully evaluated in our animal test.

We have recently published what we call an Atlas of Cancer Mortality for the United States in terms of individual counties, based on cancer deaths that occurred during the period 1950 to 1969. This is a very practical thing already. We can now determine where the so-called hot spots of cancer are in the country. By ascertaining what

is in that environment together with a demographic background of the people, we expect to have additional clues as to what does cause cancer in the individual.

FIVE-YEAR PLAN

As you know, I am sure, we have completed at least the current stage of our 5-year national cancer program plan. This was a clear congressional mandate and each year now for the past 3 years we have been providing the plan directly to the President for transmittal to the Congress. It is a plan I am very proud of because it has had wide participation from physicians at the community level and from scientists throughout the country.

It is an excellent device or road rap, to allow me to report to you and others as to what is going on in the national cancer program, and it provides, to some extent at least, a tool for setting priorities in the sense that it is reflective of the feelings of people widely disseminated throughout the scientific community.

Much has been done in terms of coordination. May I simply say that we now have six interagency coordinating committees having to do with cancer control and having to do in a very important way with environmental carcinogenesis. Last year alone, some $20 million was provided by the national cancer program to other agencies as well as to our sister institutes on the campus at NIH for studies that they do better than we, so there is no reason for us to duplicate something already ongoing.

I think this was the intent of the Congress, and I am pleased to be able to say that we have done this.

Some 20 additional anticancer drugs have been identified within the past 4 years with enough activity, in some cases very exciting activity, to justify further development for possible use in the clinic.

Finally, Mr. Chairman, as I indicated at the beginning, these are facts. This is not promise. These are things that have already been done for people. Some are not fully distributed or disseminated throughout the scientific community or the clinical community, but we are well on the way to do this. I think the momentum in the program is superb, and I believe, as do my colleagues, that the success we have had in this program is greater and has come more quickly than even I, as an optimist, would have felt was possible just 4 years ago. I pledge that we will do whatever we can to keep this momentum going.

Mr. FLOOD. How long have you been on board as Director?

Dr. RAUSCHER. Four years in May.

Mr. FLOOD. The budget before us for the Cancer Institute is $74.977.000 below the 1976 obligational level.

Dr. RAUSCHER. That is correct.

IMPACT OF BUDGET REDUCTION

Mr. FLOOD. What is the impact of that reduction?

Dr. RAUSCHER. It will obviously have an impact.

Mr. FLOOD. I think that may be the understatement of the morning.

Dr. RAUSCHER. I can describe this in specific or broad terms, but as an example in the comprehensive cancer centers, we will be unable to

award any new center grants. We will be unable to provide the kind of core or seed money to take full advantage of the network we have already set up. Mr. Chairman, we are not going to cut any single program out completely because we feel they are all very important. They have been honed down now to the best of our priorities.

But in terms of expandability, we simply will not be able to do that. We will be in a holding pattern, if you will, for some time.

Mr. FLOOD. Well, Doctor, a number of people lately tell us that we should accept this 1977 budget for cancer research and that we should increase the budget for some of the other institutes. These people tell us that we are being very shortsighted because biomedical research is being done in other institutes, that it can contribute significantly to the fight against cancer.

What is your reaction to all of these statements?

Dr. RAUSCHER. I feel very strongly that the other institutes in their activities on the campus as well as throughout the country can justify a need for more funding. I feel just as strongly that the kind of activities we have going on in the cancer program now need more dollars to be conducted in an optimal sense. In the best of all worlds, of course, I am saying that all of these forms of biomedical research are more than worthy for continuing support.

Mr. FLOOD. We understand that. But the statements are that what they are doing contributes significantly in the fight against cancer.

Dr. RAUSCHER. Mr. Chairman, I think that is true.

Mr. FLOOD. You are the Director of the Cancer Institute.

Dr. RAUSCHER. Yes; I think there is much basic research at the cellular level, conducted in other institutes, that has a chance of contributing to cancer. But it should be pointed out, also——

Mr. FLOOD. Chance?

Dr. RAUSCHER. A very good chance of contributing to cancer as well as to other diseases. I think it should be pointed out, however, that the NCI, more so than at any time in its history, is supporting basic research which in turn will contribute to the understanding of other diseases as well, not only to cancer but to others.

I think it is a two-way street. Some of the work being done by other institutes is so good, as I said before, we have been willing in the last 4 years to put——

Mr. FLOOD. So good with reference to your institute?

Dr. RAUSCHER. It is studies on the differences between the normal and diseased state and whether that diseased state at the cellular level is cancer or cells infected with an influenza virus, as an example, and that information should be applicable to more than one disease. It is truly a team approach at NIH.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

Mr. FLOOD. Last year in our report, that is on the 1976 Labor-HEW appropriation bill, we directed—I use the word "directed"—you to, let me quote from language in our report.

> Work closely with the National Institute for Occupational Safety and Health in initiating that institute's occupational carcinogenesis program and to provide direct support for this important program.

All right: what direct support have you provided to date, and on what projects are you jointly working?

Dr. RAUSCHER. Some of the examples that I provided in my opening remarks, such as the identification of seven new chemicals in the past 4 years, that kind of identification and the reporting to the FDA, and NIOSH, in particular. We do those kinds of studies with funds that you provide to the Cancer Institute.

I have met this past year with Dr. Finklea on four occasions. This has resulted in the cosponsoring, that we funded, of several symposia, one in particular I can remember very vividly. It has resulted in Dr. Finklea's developing a plan whereby some of the grants going to his agency are now being funneled into the Division of Research Grants at the NIH, where some of those grants will be directed to the National Cancer Institute for funding.

In addition to that, some of our solicitations for grants are now being provided to that agency for perhaps their direct funding or for funding with dollars that we would provide.

Mr. FLOOD. Is it your position that you are complying with this directive from the committee?

Dr. RAUSCHER. Yes, sir, it is

Mr. FLOOD. What do you plan in the future, other than what you just stated more than conversations with the Director—funds, etc.?

Dr. RAUSCHER. If this is the best way to do it, it will continue to be funded directly. It will certainly be prompt information on any chemical that we determine is carcinogenic, especially those that affect people at the work place.

Mr. FLOOD. Do we understand you are committing yourself and your Institute to this close cooperation with NIOSH from now on?

Dr. RAUSCHER. Yes, indeed.

ENVIRONMENTAL CAUSES

Mr. FLOOD. More and more evidence is coming to the surface linking as much as 70 to 80 percent of all cancer to environmental causes. What percentage of the 1977 budget will be devoted to researching the environmental causes of cancer?

Dr. RAUSCHER. If you exclude viruses, as many people do when they talk about environmental carcinogenesis——

Mr. FLOOD. What are you talking about?

Dr. RAUSCHER. Here I would be talking about chemicals, and radiation, predominantly chemicals. That would be of the order of 17 percent of the total budget. Mr. Chairman, that does include not only the direct funding of the operational aspects of grants and contracts, it also includes such things as training, construction and the like.

Mr. FLOOD. Seventeen percent, is that a lot, or isn't it?

Dr. RAUSCHER. I think it is a lot.

Mr. FLOOD. That is not a small percentage?

Dr. RAUSCHER. No; it is not. Let me explain what I mean.

I agree with the statement, and I have used it many times myself, that 70, 80, 90 percent of our cancers are extrinsic and environmental. I think the important question is what proportion of that percentage of our cancers are caused by things we know nothing about.

As an example, no more than 4 percent of cancers occur because of a worker being exposed in the workplace. We know that 40 percent, a

full 40 percent of our cancers are caused by tobacco or tobacco together with alcohol.

Mr. FLOOD. Together with alcohol?

Dr. RAUSCHER. Alcohol is a potentiating factor for head, neck, colon cancer, pancreatic cancer, and the like. So we are getting down to something like 20 to 30 percent of our cancers are occurring because of things we know nothing about, and I believe that $122 million devoted to that kind of thing is good.

Mr. FLOOD. Well now, in view of the volume of new evidence on environmental causes of cancer, you say 17 percent of your 1977 cancer budget is a proper figure?

Dr. RAUSCHER. It is 17 percent, I believe, for the basic studies and the identification studies of chemicals that we are charged with. Seventeen percent is a good figure.

FREDERICK CANCER RESEARCH CENTER

Mr. FLOOD. We are now in the fourth year of operation of the Frederick Cancer Research Center; is that right?

Mr. RAUSCHER. Yes.

Mr. FLOOD. This is a contract with the Litton Bionetics Corp.; right?

Dr. RAUSCHER. That is right.

Mr. FLOOD. How much do you have in the 1977 budget to support that contract?

Dr. RAUSCHER. It will be of the order of $26 million.

Mr. FLOOD. How much have you spent to date on that contract, from the very beginning?

Dr. RAUSCHER. About $94 million.

Mr. FLOOD. As I understand, the mission of the Frederick Center is to test the chemicals ordinarily found in the environment.

Dr. RAUSCHER. That is one of the purposes; yes. There are 12 different tasks and that is one.

Mr. FLOOD. How long does it take and how much does it cost to test each chemical?

Dr. RAUSCHER. It costs about an average of $100,000. It takes 2½ years, and many hundreds of animals to test one chemical.

Mr. FLOOD. Having completed the test of these chemicals, have you publised reports on each and every chemical, not "we think," but a report on each and every chemical you have fully tested?

Dr. RAUSCHER. Yes, indeed. Those that have been fully tested, analyzed for pathology and biometrically analyzed, we have published full definitive reports in the Federal Register and hand-carried to the regulatory agencies.

Mr. FLOOD. We want that information for the public on each one as soon as possible.

Dr. RAUSCHER. I agree.

Mr. FLOOD. How do you transmit this finding you make to the EPA and other agencies?

Dr. RAUSCHER. There are three ways. First of all, we do publish our memoranda of alert, as it was formerly called, when all of the analysis is done. This is hand carried on a particular day to all of the Federal agencies involved.

Second, we publish this in the Federal Register, not only for the agencies, but for the public at large, and, third, I have established four interagency coordinating committees in which people from EPA, FDA, NIOSH, OSHA, and other agencies, meet with us once a month so they are constantly apprised of what is coming down the pipeline.

Mr. FLOOD. How does your institute decide which chemical to test?

Dr. RAUSCHER. We have several grants and one contract in particular with the Stanford Research Institute called a ranking contract. We determine which of the 200,000 new chemicals produced every year are apt to contaminate the environment, apt to be added to a product that the housewife in a home is exposd to, as an example. All kinds of factors go into ranking what might be hazardous.

We take a look at the chemical structure, and if it is close to a known carcinogen, that elevates it to top priority. There are many things that go into the determination.

VIRUS ISOLATION

Mr. FLOOD. Last year, you will recall, you made quite a point in telling us "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." We were hoping to read something about this program, something about this report, but we couldn't find any specific reference work in the material you sent to the committee.

What do you have to report on this?

Dr. RAUSCHER. I have it here prominently in my highlights. That is still in the area of promise, so I didn't mention it. It continues to be as exciting as last year. As a matter of fact, it has been confirmed now on three occasions so it is a solid piece of scientific evidence. The virus is growing and growing well. We are still in the process of determining whether people who have acute myelogenous leukemia have infections with the virus as determined by a biochemical marker, we call it, or antibody to it.

If we can show a differential in terms of the diseased versus normal, we will have much better evidence that the virus may be cause and leukemia, the effect. These studies will take, I think, another 2 or 3 years before I can tell you whether it is a bona fide inducer of cancer in man.

Mr. FLOOD. Last year, you told us that this virus could be found in nonhuman primates. Is the shortage of the research animals hampering your work in this area? We heard about a shortage in the last few months. So what do you do about the supply of animals?

Dr. RAUSCHER. Many of my colleagues are concerned with the shortage of certain species of nonhuman primates. We are trying to breed some of these, ourselves. We are trying to negotiate further with suppliers in different countries to allow us to get, if not animals used directly for research, at least breeding stock so we can build up our own supply in this country. It is a problem.

Mr. FLOOD. That is why I asked you. Again, are you assuring a supply? What is anybody doing to assure a supply of these animals for this research?

Dr. RAUSCHER. With cancer it is primarily the breeding colonies; NIH has four or five of its own breeding colonies, and we are getting

a good supply of animals from there, but we think it is unethical to even request some of the endangered species, such as gibbons, caught directly from the jungle. What we would like to do is better be able to breed these animals; thus, in future years we will not depopulate that endangered species and will also have some for our own use.

EPIDEMIOLOGY

Mr. FLOOD. It appears that you are expanding your epidemiology activity. We see that the Center for Disease Control has a Cancer and Birth Defects Epidemiology Unit. We see the National Institute for Occupational Safety and Health has an epidemiology unit, and I suppose there are others.

How do all of these units coordinate their efforts?

Dr. RAUSCHER. One very effective way is by exchanging personnel. Dr. Sencer at CDC has assigned two of his people directly to our program. We in turn then not only provide training for his people but also provide some of our people to him.

Secondly, we have, as I mentioned, these interagency coordinating committees, and Dr. Sencer, or his people, in some cases epidemiologists, serve on these coordinating committees so in meeting once a month in some cases we can tell one another what we are doing. We also provide funds directly to CDC for this kind of work.

Mr. FLOOD. What happens to the data that these various units generate?

Dr. RAUSCHER. The data are very often published in the open literature, or in the case of our epidemiology branch, perhaps the county mortality data were published as an atlas. This is provided widely to the scientific community as well as to the public.

Mr. FLOOD. How much of all of your epidemiology work do you contract out? Give some examples of the contract work.

Dr. RAUSCHER. It is on the order of about $11 million for epidemiology at the present time through grants and contracts. Another $3.8 million is used directly in-house. Good examples of contracting out or granting out would be the migrant studies. This is one of the principal pieces of information that allow you and us to say that 80 percent of our cancers and extrinsic.

This study showed that the Japanese male in Japan has a high risk to stomach cancer. When he moves to this country, his risk goes down to yours and mine. The American white male is amongst those who have the lowest risk to stomach cancer in the world. That is an example.

Mr. FLOOD. Does any of this epidemiology contract work overlap with the work at the Center of Disease Control and NIOSH?

Dr. RAUSCHER. We don't think so. It is done in a very complementary way. If there is one thing I would like to increase in the country, it would be studies in epidemiology. There simply aren't enough people to do the work we feel has to be done. We provided about 6 months ago another $3 million for cancer epidemiology, and we advertised widely throughout the country and asked the epidemiologists to come in and tell us what they would do with that money to help us with cancer surveillance. We got only $2.2 million worth of applications, and it is likely about $1.2 million of that will be good enough to fund.

CANCER CENTERS

Mr. FLOOD. How many comprehensive cancer centers do you have operational at this time? And what percentage of the total population is covered by them?

Dr. RAUSCHER. We have 17 identified and operational at the present time, and an additional four are in now for recognition. We have, with the 17 alone, about 106 million Americans within 120 miles of a center, including the community hospital network attached to each center, so it is over half of the population at the present time.

Mr. FLOOD. The Cancer Act, itself, requires the cancer centers to engage in outreach or community activities in order to assure complete cancer care for the patient. How do these centers carry out that kind of responsibility?

Dr. RAUSCHER. They do it in several ways.

Mr. FLOOD. People keep telling us that cancer control programs do not receive adequate attention from the centers. What about it?

Dr. RAUSCHER. Cancer control is another issue here, but the way the centers operate is essentially as quarterbacks within local areas. A local area could be a major city or State, for that matter, and they try to provide expertise such as an example through dosimetry monitoring of radiotherapy used in community hospitals; so every one is working on common protocols or are using doses that are equivalent one to the other for comparison. Many of the centers also now have Cancerlines or telephone networks for advice to physicians and to lay people.

For instance, M. D. Anderson in the Southwest, in Houston, Tex., has a dial access system whereby physicians from 18 Southwest States call in and find out the latest information for a particular kind of cancer.

We are doing this also in terms of information dissemination from laboratories in Wisconsin, and from laboratories in Chicago, as just some examples.

Dr. RAUSCHER. A major service is referral privileges. If there are patients, such as children with acute leukemia, that require sophisticated monitoring, bone marrow scans and the like, these patients can be referred by the community doctor into the center. In this regard, Mr. Chairman, community doctors continue to be our first line of detection and defense for the cancer patient and for the prospective cancer patient.

Other services would be that experts within the comprehensive center will go out to the community hospital and help the local physician as to how best to take care of a particular patient. There are many examples of this.

Mr. FLOOD. How do you determine if the comprehensive cancer centers are effectively reaching out to the general population?

Dr. RAUSCHER. We have a very detailed scheme of evaluating a center which I think it is a very effective. I will be glad to submit examples of how we do this for the record.

QUESTIONNAIRE FOR EVALUATING CANCER CENTERS

Each comprehensive cancer center is evaluated at least every 3 years by a site visit team composed of outstanding scientists and administrators selected not only for their experience and expertise in their field of interest, but also for their knowledge of the management of large centers. After collecting informa-

tion firsthand, the site visit team is charged with making a series of judgments as to whether the center is in compliance with the 10 characteristics of a comprehensive cancer center as set by the National Cancer Advisory Board. Characteristic No. 4 specifically deals with the ability of the center to influence the surrounding community and to provide direct people benefit in the area of cancer diagnosis and treatment. Seven general statements relative to the various degrees a center may be effectively reaching out to the general population have been developed by the National Cancer Institute. To aid reviewers in evaluating the center and in selecting the general statement which most closely reflects the status of the cancer detection program at the center, a set of questions are provided to serve as tools in obtaining detailed information needed. The general statements are given below and are followed by examples of the types of questions asked by reviewers in evaluating a center.

CHARACTERISTIC NO. 4 (GENERAL STATEMENT)

The center should have or should develop an organized cancer detection program.

The cancer detection program of this center and affiliated programs has been developed to reach the majority of all potential cancer victims within the region served, at a realistic cost.

The cancer detection program of this center will certainly reach a large number of potential cancer victims in the region served, and appears to be economically sound.

The cancer detection program of this center is adequate in terms of cost and design for those individuals being screened.

The cancer detection program of this center is limited, but there is evidence that significant improvements will occur in the future.

The cancer detection program of this center requires better management and the application of a more realistic economic approach.

The cancer detection program of this center is very limited and must be expanded to serve more adequately the region's needs.

The cancer detection program of this center is limited, as presently structured.

EXAMPLES OF QUESTIONS ASKED AT CENTERS (FOR EVALUATION)

(*a*) Is the detection program of the center innovative with respect to the application of new techniques, and insuring a cost-effective approach?

1. Does the cancer detection program deal with more than one cancer? All major cancers?

2. Have any innovative modifications of existing methods been developed at this center?

3. Are any new methods/techniques currently in a field-trial stage? If yes, identify methods/techniques and describe the nature of the field trial to date.

4. Have the new methods/techniques come from research accomplished at this center? Or are they based on research results from elsewhere?

5. What methods are being used to assess the cost-effectiveness of the detection methods/techniques? Are up-to-date financial records of the cost of the cancer detection program available?

6. Has the center involved the majority of the health providers in the region in their program to insure maximum utilization of existing resources?

7. Are paraprofessionals utilized in the detection effort in order to lower the cost?

(*b*) Is the cancer detection program designed to have a significant impact on both the public and professionals throughout the region served by the center?

1. What has been the role of health professiona's throughout the region in planning this detection program? What is (and will be) the role of health professionals and paraprofessionals throughout the region in carrying out this detection program?

2. What is (and will be) the role of health professionals and paraprofessionals in the center in carrying out this detection program?

3. Has the center been effective in mobilizing additional community resources (that is, space, funds, volunteer workers, et cetera) necessary to support such a program? Is the cancer detection program closely coordinated with volunteer agencies, such as ACS, in the region?

4. Are the cancer detection programs of the center evenly distributed throughout the region?

5. What education-communication materials and procedures are being used to motivate the public to be responsive to this program? How will these be updated, modified, et cetera? For health professionals?

6. What is the procedure for assuring that, when precancerous and/or cancerous lesions are detected, the patient will be moved into a definitive diagnosis-treatment situation?

7. Is the program designed to target high-risk population groups?

8. Is the program designed to be self-sufficient on a fee-for-service or other basis after demonstration?

(c) Does the cancer detection program have a sound statistical base for the purposes of evaluation of results?

1. Is the statistical base a population-based cancer reporting system? What is the population of the region served by the center?

2. Will the statistical base provide information on the epidemiological and demographic characteristics of the total cancer problem in regions served by the center?

3. Will the statistical base provide information whereby high-risk groups can be identified in the region?

4. Is cancer a reportable disease in the State(s) in which the center's region is located? If yes, how effective is the reporting of cancer by health professionals in the region? Does the center take an active role in promoting the reporting of cancer by health professionals?

5. Is these evidence that biostatisticians and epidemiologists are involved in developing the new cancer detection program?

6. Is there evidence the center's cancer detection program has made a significant impact on cancer mortality in the region served?

7. Is the statistical base in support of the cancer detection program automated and readily accessible?

RESEARCH RESULTS INTO PRACTICE

Mr. FLOOD. All of your research findings must reach the medical practitioners if they are going to be useful. What efforts, besides those of the cancer centers, are you going to support in 1977 to insure the transition of all these research results into effective clinical practice?

Dr. RAUSCHER. Yes; I assure you we will. Again we are doing this through the comprehensive cancer centers program, with support in particular through our cancer control program. We spent about $57 million in that program in fiscal 1976. A significant proportion of that had to do with transmitting research findings to the practicing physicians throughout the country. We are training different kinds of paramedical people as well as continuing education for the physician in such things as cancer interventions including rehabilitation of the cancer patient. This is something we never did before, as you know, just a few years ago. But we are doing it now.

POSITIONS

Mr. FLOOD. In your budget justification you state that you were provided 71 new positions in 1976. We authorized over 130 positions for your institute. What happened to the others?

Dr. RAUSCHER. The 71 positions were received since the hearings last year. We haven't gotten any new positions that were included in the 1976 appropriation yet. But I think, as Mr. Miller mentioned yesterday, we anticipate being able to recruit for all positions that the Congress allowed this year.

Mr. FLOOD. What does that mean?

Dr. RAUSCHER. In our case it will be about a net of 79 to 80 positions.

Mr. FLOOD. What is the problem?

Dr. RAUSCHER. We have not been authorized to recruit for those yet. I don't think anyone at NIH has yet received their allotment of new positions, but we anticipate this within the next couple of weeks.

TRAVEL

Mr. FLOOD. You are asking for $3,423,000 for travel, and that amounts to $1,813 per position. We compared your figures with the Heart Institute, and you are up 50 percent, and we compared with the Arthritis Institute, and you are up 200 percent. Why is your agency so much above the others?

Dr. RAUSCHER. The principal, if not the entire reason is that we rely very heavily on what we call our special ambulatory care program. Much of cancer research with patients can now be done on an outpatient basis. It is cheaper for them, and it is cheaper for us than to keep them in the hospital.

Mr. FLOOD. Isn't this true of the other institutes?

Dr. RAUSCHER. No; but it certainly is for cancer. We use several motels in Bethesda where we put patients and families up, bring them in and out so we can study their diseases as outpatients rather than hospitalize them.

Mr. FLOOD. Are you talking about monitoring grants and contracts?

Dr. RAUSCHER. No; this is just for bringing patients, or volunteers, but primarily patients, into Bethesda. We treat them, evaluate them, monitor the patient as an outpatient rather than, again, hospitalize them. We have a chance of seeing many more patients than before, about 124,000, as I recall, last year, and many of these have to fly back and forth to their homes.

Mr. FLOOD. Last year, the committee stated in its report on the 1976 bill that it was appropriated only $2,900,000 for travel to your institute. Now I see you intend to spend $3,100,000 for travel in 1976. Do you think we were kidding when we put that in the report, or what?

Dr. RAUSCHER. Not at all, sir. This is due to two reasons. The cost of air transportation and other forms of transportation has gone up, so partly it is that. Partly it is because we continue to believe that we can study more patients effectively on an outpatient basis and their travel is a large part of that. We thought your reference to travel was for staff travel and not for patient travel.

NUTRITION

Mr. FLOOD. What is the goal of your cancer and nutrition research program?

Dr. RAUSCHER. Nutrition has two major thrusts. One is to determine whether by modifying the diet we can keep patients alive and in a better state longer while they are undergoing such things as chemotherapy or various treatment. Many mothers of leukemic children have talked to me personally, as well as our physicians, to say, "How can we keep my son on chemotherapy from being sick in the stomach all the time?" This can be a dreadful situation in many patients. We can help more parents and children better than we have. As a matter of fact, we have pamphlets out available for parents of leukemic children and children with other forms of cancer, specifically those

undergoing treatment. We also want to find out more about possible carcinogenic effects of nutrition.

Some investigators in the country now feel that nutrition or diet by itself, not contaminated with pesticides or other substances, but a high fat diet, may be carcinogenic, contributing to the high rate of colon cancer in the United States. In Japan it is low. This difference is possibly due to a difference in diet.

We want to find out about such things as nitrates and nitrites in our foods. Does the way our bacon is cured cause cancer in people?

Mr. FLOOD. Will you be eventually able to provide the public with a list of these dietary things that might be associated with cancer in certain persons?

Dr. RAUSCHER. That is one of our major goals; yes.

Mr. FLOOD. Suppose you summarize for us the results of your symposium last spring, the role of nutrition in the causation of cancer.

Dr. RAUSCHER. Well, there are many people now who believe that as many as 25 to 30 percent of cancers are related to nutrition. These are cancers of some major types; for instance, obese women have a higher risk to breast cancer than nonobese women. This may have something to do with hormonal influences in the body, so diet is an indirect factor. Cancers of the head and neck, of the esophagus, of the small and large bowel, of the rectum, of the stomach, may well be related to the fat content of the diet or it may be related to abrupt changes in diet. An example is the Japanese moving to this country and running out of his Japanese food that he brings with him and changing to an American diet.

There is some evidence, although not much, that such contaminants as pesticides may contribute to cancer. You know that diethylstilbestrol is a known cancer inducer in female children born to mothers who took it during their pregnancy to prevent spontaneous abortion.

Some livers, beef livers that people eat, still contain a residue of DES. Most of us feel that this amount of DES is too small and infrequent, that it probably doesn't significantly contribute to our cancer burden. But it is a known cancer inducer, and we have to be wary of it.

BREAST CANCER SCREENING AND DETECTION

Mr. FLOOD. What are the results so far of this breast cancer screening and the detection program?

Dr. RAUSCHER. That has been very heartening.

Mr. FLOOD. Are you planning to expand this program?

Dr. RAUSCHER. We plan not to expand it in the sense of increasing the number of centers above 27, but we are doing two other things. We are planning to make arrangements whereby additional women can be brought into each of those 27. We are now evaluating about 230,000 American women. These are demonstration projects. When something has been demonstrated at the local community level, our intent is to encourage the local community to continue the service through third-party coverage, or perhaps through national health insurance, and move that expertise into some other part of the country to demonstrate to that community and those physicians that it can be done well.

So we don't feel a need to go beyond 27 but rather to reshuffle, if you will, inevitably those 27.

Mr. FLOOD. How many women will ultimately benefit from the program?

Dr. RAUSCHER. Directly through the program on the order of 250,000 women will have, at no expense to them, at least physical examinations and mammograms. There will be several followups in succeeding years and then we will follow that group of women for something like 10 to 12 years to find out whether in fact early diagnosis will result in longer life. We have every reason to expect this is true, but we want to prove it.

Throughout the country, the spinoff and magnetizing effects are so great that many more million women are now coming in to their local physicians and hospitals where they pay for their mammograms, as a result in part, at least, of the publicity of this program and certainly of prominent people recently who have developed breast cancer.

Mr. FLOOD. What is your evaluation of the publicized studies suggesting a possible link between the estrogens for postmenopausal women and the apparent rise in the incidence of cancer in this same group?

Dr. RAUSCHER. There is very little evidence that this kind of thing affects breast cancer, but it does affect uterine cancer. We are concerned about this, and it has been a longstanding study on the part of scientists here and abroad.

The issue here, Mr. Chairman, is a fascinating problem in biology. We still don't know whether estrogens, and there are many, are carcinogenic by virtue of their being estrogens. If they are carcinogenic, as an example, all women and all men are probably at some burden because of naturally occurring estrogens. That is why we are so concerned about the balance and effect that diet may have on these balances. If estrogens are carcinogenic because they have a certain chemical structure, it probably isn't going to do the public any good to protect them from DES, as an example. That is a very key series of experiments still ongoing.

FLUORIDATION

Mr. FLOOD. A very distinguished Member of the House and very old friend of mine, Mr. Delaney from New York, has been concerned about fluoridation, as you know. He started this thing a number of years ago introducing legislation. He has been after it and after it. He has been after you, the committees, the legislative committees, and everybody on this problem.

He asked me to ask you several questions. He asked me to have these questions submitted to you at this hearing today and have these answered in detail. We want you to do that for the record and send a copy of the questions and answers to Mr. Delaney.

[The information follows:]

QUESTIONS SUBMITTED BY MR. DELANEY OF NEW YORK

Question. How long has the U.S. Public Health Service, of which the NCI is a part, been "endorsing" artificial fluoridation of drinking water?

Dr. RAUSCHER. On April 24, 1951, the Surgeon General of the Public Health Service, Dr. Leonard A. Scheele, in his testimony before the Senate Subcommittee on Appropriations stated the water fluoridation policy of the Public Health Service. His statement was as follows: "During the past year our studies progressed

to the point where we could announce an unqualified endorsement of the fluoridation of public water supplies as a mass procedure for reducing tooth decay by two-thirds."

Question. What role has the Division of Dentistry, H.R.A., played in the fluoridation-cancer controversy?

Dr. RAUSCHER. The preventive dentistry functions, including fluoridation, have just recently been transferred from the Division of Dentistry to the Dental Disease Prevention Activity of the Bureau of State Services, Center for Disease Control. During the time the Division of Dentistry was responsible for the functions in the area of fluoridation, their role was to request from the National Cancer Institute detailed information regarding questions about any alleged association between fluoridation and cancer.

Question. Is the National Cancer Institute aware of studies other than those conducted by Drs. Dean Burk and John Yiamouyiannis which have linked fluorides or fluoridation to cancer-causation?

Dr. RAUSCHER. Yes, we are aware of other reported studies in this area. Over the course of the past several decades, there have been various suggestions in the literature that there was either laboratory or human evidence of a link between fluorides and cancer. All of the published systematic studies of this exposure in humans have failed to support these suggestions. Perhaps the most recently reported study is that of Dr. Kinlen of Great Britain published in the British Dental Journal in March 1975.

Question. Had the National Cancer Institute ever investigated the possible carcinogenic effects of fluoridation before 1975? If so, cite and provide the articles which the agency has published on this matter.

Dr. RAUSCHER. The National Cancer Institute did not conduct any new studies prior to 1975 because much data were available from studies of other U.S. agencies such as the Division of Dentistry as well as from other countries. In view of this and in view of the multitude of other factors which must be tested it was felt, and I believe rightly, that yet another retest would be costly, overduplicative and again confirmative of information already on hand. Your concern, sir, has once again been of benefit towards assurance of the American people and others that fluoridation is noncarcongenic, and has drawn attention to the fact that fluoridation helps prevent dental carries—probably the most prevelant disease in Americans today. Because of your concern, the National Cancer Institute in 1975 sought to evaluate the best and most up-to-date epidemiologic data comparing the cancer experiences of people in fluoridated and nonfluoridated U.S. communities and (very importantly) in people of the same communities before and after fluoridation. We are again convinced, as are scientists of other countries, that natural or deliberate fluoridation does not result in increased risk of peoples to cancer.

Question. Why did the National Cancer Institute continue "to stand by its previous statements" in public remarks regarding water fluoridation and cancer after August 1, 1975, without making any mention whatsoever of its "then-in-progress" study of this matter?

Dr. RAUSCHER. National Cancer Institute officials included a description of the NCI fluoridation study in responses to inquiries from the public while the study was in progress, including the months from August to November, 1975, when the study was completed and made available.

Question. Why were the findings of the NCI study, "Fluoridated Drinking Water and the Occurrence of Cancer," released to other Government agencies and thence to the general public—even for use in influencing referenda on the fluoridation issue—long before being submitted to the U.S. Congress and others who had requested it?

Dr. RAUSCHER. The findings of the NCI study of the relationship between fluoridation and the occurrence of cancer were clear by the latter part of October, even though the manuscript reporting the study had not been completed. It is customary during the course of on-going NCI studies, information is provided to other Federal agencies if they need such information to fulfill their own responsibilities. In this case information on the fluoridation study was provided only in response to requests from such agencies several weeks prior to the manuscripts completion.

Information submitted to Members of Congress and the public has generally been in the form of a completed document. With respect to the fluoridation study, the manuscript of the report was completed on November 13, 1975, and delivered the following day to Mr. Delaney and other Members of Congress who had requested it. The availability of the report was announced several days later to the press and public.

Question. Why did the NCI choose 5-year intervals rather than yearly statistics in formulating their "November study" and making subsequent remarks?

Dr. RAUSCHER. When the National Cancer Institute first put together our system of cancer mortality by county, we contemplated the desirability of looking at time trends. Since most of the 3056 counties within the United States do not contain populations large enough for stable estimates of site-specific mortality rates by individual year, we decided to group the deaths into 5-year intervals. The NCI publications which have investigated time-trends have done so using these 5-year intervals. We are confident that these analyses have been appropriate for testing the hypotheses we have investigated.

Question. The NCI was previously requested to supply this subcommittee with a "substance point-by-point scientific response" to the data and analyses presented in the studies by Drs. Dean Burk and John Yiamouyiannis which were submitted to Congressman Delaney on July 8, 1975 and December 11, 1975. The major criticism of the Burk-Yiamouyiannis studies by the NCI appears to be in the use of demographic variables. Dr. Rauscher stated: "Differences in the trends in the uncorrected rates can be attributed to differences in the racial and age composition of the populations involved" (letter to subcommittee: February 13, 1976).

The NCI is requested to supply this subcommittee with all the data upon which the variables of age ("over 65 population") and race ("non-white population") were based and to give the specific step-by-step procedure the agency used in correcting for demographic variables.

Dr. RAUSCHER. All of the data, on which the most recent critique and analysis of the Burk-Yiamouyiannis study was based, was obtained from the extensive publication covering 1950, 1960 and 1970 decennial Census of the Population and from the Annual Reports of Mortality published by the National Center for Health Statistics. The shift in age (a greater percentage of the population over 65), for the cities cited, is well documented in the above referenced publications. The same is true for the racial shift (a greater percentage of non-whites, particularly blacks) in the population of these cities. This was pointed out to Drs. Burk and Yiamouyiannis and they were repeatedly urged to consider this variable. It was also discussed in detail with Dr. E. Deming (statistical consultant to the National Health Federation), who stated that he advised Drs. Burk and Yiamouyiannis to carry out this procedure. I again urge them to avail themselves of the same data we have used.

Question. Upon what data is the agency's constant reference to "standardized mortality ratios" based? The NCI is requested to give the specific step-by-step procedure it has used in formulating these so-called "SMR's."

Dr. RAUSCHER. SMR determination is a widely accepted technique for standardizing mortality data [1] in order to control for variables. It then permits comparisons between more nearly alike groups among sub-sets of the population. In other words, it refines the data to which it is applied, thus giving greater confidence in the importance of any remaining difference or lack of difference, for the test variable; in this case the effect of artificial fluoridation on the occurrence of cancer.

Mr. FLOOD. Mr. Michel.

Mr. MICHEL. Thank you, Mr. Chairman.

I assume you had some questions in that area that you were going to submit for the record, because I know there have been some inquiries made to your office, Dr. Rauscher, that I think probably deserves a response. Personally I have been one of those who supported fluoridation of water, and the Dental Institute tells us it results in a 60 percent reduction in dental problems. I look at that as very positive.

[1] Found in elementary text books of biostatistics. Ref: "Principles of Medical Statistics," Bradford Hill, 8th Ed., 1966. "Standardized Mortality Ratio. The ratio of deaths at all ages observed in a given population to the deaths that would have occurred in that population if in each age (and sex) group it had been exposed to some selected standard rates. Rates of mortality and morbidity are usually affected considerably by the age, and to a slighter extent by the sex, constitution of the populations concerned. The comparison of crude rates at all ages is therefore likely to be misleading as a measure of the mortality, or morbidity, experiences prevailing in relation to such features as the sanitary environment. Some form of average of the death-rates at ages is required which allows for the fact that populations differ in their structure. This average is customarily reached by a process of standardization, a process which leads to a weighted average and thereby to more comparable indices."

On the other hand, nobody has yet proved to me that the pluses don't outweigh whatever losses there might be, but I think there could very well be some danger to which we aren't currently apprised, and if there are, I guess we should know about it.

Dr. RAUSCHER. We simply see no evidence for any deleterious carcinogenic effect on the population. I think in this sense Mr. Delaney and his colleagues have done all of us a good turn by making us take another look at existing data, new experiments and data from new experiments. At the present time, however, we simply don't see any evidence that fluoridation puts man at risk to cancer.

I know our colleagues in the United Kingdom agree. Recently the British College of Physicians said:

> There is no evidence that fluoride increases the incidence or mortality of cancer in any organ.

Mr. FLOOD. If that is a majority opinion, there is a strong vocal minority.

Dr. RAUSCHER. I understand. We will provide a summary of all that we have for the record.

Mr. MICHEL. I think some of that comes from the fact that they take statistics from an area where fluoridation is used but doesn't take into account all the other environmental aspects that exist in that community that really make the incidence of cancer higher than in a community where you just don't have those pollutants and whatever in a large industrial city.

Dr. RAUSCHER. It is ethnic background, age, sex, and so forth.

POSSIBLE CARCINOGENS

Mr. MICHEL. Doctor, the reference in your statement to the possible reuse of cyclamates leads to the question whether we sometimes jump to conclusions regarding possible cancer-causing agents before all the research is in. Does that concern you?

Dr. RAUSCHER. It concerns me very much. The problem is in the sensitivity of test systems that we use. I said before, it takes something like $100,000 and 2½ years to test one chemical, but these are relatively gross tests. It is a difference between malignant tumors in the treated group versus untreated groups. Now we are looking at all tumors, malignant and benign, for comparison, but if you have a weak carcinogen, the chances are unless you use 50,000 animals per test—and we usually use 400 to 600—you would have to get up to thousands of animals per test to pick up a weak carcinogen, and it is almost impossible to do this when in fact you have to test 500 to 1,000 chemicals a year. It would take all of our budget.

Mr. MICHEL. When I was over in Sweden a number of years ago, I went to the Karolinska Institute, where they had all these rooms and rooms of test animals. Do they follow about that same pattern? You say you use 400 animals?

Dr. RAUSCHER. Depending on the test. It is 400 to 600 animals to a test, and it is that way throughout the world. George Klein, at Karolinska, and his colleagues, would do the same thing; yes.

Mr. MICHEL. There sometimes seem to be reports coming out of the Cancer Institute talking about an agent being cancerous when it may

have produced cancer in one or two animals or so, and this tends to alarm the public and produces some adverse economic impact. Do you make any effort to try to firm up some of these findings before releasing them to the public?

Dr. RAUSCHER. Yes, we do, and we are doing more of that than in the past. In the past the only way to firm up that kind of thing, especially if it was a very weak possible carcinogen, was to repeat the experiments. That means you are another 2½ to 3 years down the road before you get an answer to the question.

What we are trying to do now is to put more animals on study at the first time material is tested. In some tests we are now using two different species instead of just the mouse. In some cases the rat is used as well as the mouse. But more importantly, we are using more doses than we did before. We are giving the animal as much as it can tolerate without death due to chemical toxicity.

The problem of confirmation of a borderline carcinogen is one of expense and primarily of time, meaning 2½ to 3 years. Trichloroethylene is a good example where it had a deleterious economic impact even though it is really a weak carcinogen.

ENVIRONMENTAL CARCINOGENESIS

Mr. MICHEL. Is it true 85 percent of cancers are environmental-induced?

Dr. RAUSCHER. We think at least 85 percent. There are things in the environment, as you know, that induce cancer more than one's genetic stock.

Mr. MICHEL. Now, as I understand it, only about 10 percent of your Institute's budget, however, goes for environmental concerns while a great proportion of the budget is directed toward treatment research. Does this indicate there is perhaps a need to reorder budget priorities?

Dr. RAUSCHER. I think there is always a need to reevaluate priorities. We are spending about 17 percent of our money, including the cost of management, construction, training, as well as operational expenses, on environmental carcinogenesis, excluding viruses, which many people would include. We do not, because I believe most people think of chemicals when they talk about environmental carcinogenesis. The key question here is not, as I think we mentioned a bit before, not whether 80 or 90 percent of the cancers are extrinsic, but what portion of those cancers are caused by things we know nothing about. We know that about 40 percent of our cancers are related to tobacco and alcohol; we know another 10 percent are related to occupational or local environmental impacts; possibly some to diet.

So what I am saying is I think that 17 percent of our budget on nonregulatory things is adequate. That is the other point. We have no regulatory authority or mandate, so we are spending a full 17 percent of our budget on the research aspects, on the identification of carcinogenesis aspects of all cancer. If we had regulatory authority, or mandate, 17 percent would be grossly inadequate. I agree. All I can say is that for projects in environmental carcinogenesis last year, we paid about 62 percent of approved grant applications coming into the NCI. The carcinogenesis program is of high priority.

SUPPLEMENTAL GRANTS

Mr. MICHEL. With respect to your grants, you have some listed as supplemental. What is a supplemental grant? Why are they awarded?

Dr. RAUSCHER. Let me give an example. In clinical trials, we have 23 clinical cooperative groups in the country, groups of physicians that get together to treat patients according to common protocols and then compare the results in terms of determining whether treatment of schedule B is better than A. When adriamycin came along, it became apparent very quickly, during the middle of a budget year, that it was going to be one of the best drugs we had. So we provided additional funds—supplemental funds—in the middle of a budget year to get some of the people in the country using adriamycin, for which they had no dollars.

COORDINATION

Mr. MICHEL. You also mention the efforts that are being undertaken to coordinate your efforts with other Federal agencies, and referred to the Federal Interagency Coordinating Committee. What exactly is the nature of that collaboration?

Dr. RAUSCHER. Well, a good example of this is your question before, sir, and that is what do we do to inform agencies as well as the public in terms of possible carcinogens coming down the road. There are some 18 Federal agencies that have something to do one way or the other with cancer research or cancer control.

The act of 1971 charges me to be a coordinator, at the very least, of cancer research in the Federal Government. So we have gotten these people together. We meet about once every 4 months to find out what each of us is doing. When it has to do with chemical carcinogenesis, I have a subgroup to consider that.

All of the health agencies within HEW, as well as also EPA, NIOSH, OSHA, sit down once a month to take a look at the raw data coming in on the test of a particular chemical. So they do not have to wait 6 months to a year after the data comes off to find out what is carcinogenic. They know on a month-to-month basis. That is what I mean by an interagency coordinating committee. It is avoidance of unknowing duplication, and a sharing of important information on a timely basis.

TOTAL CANCER FUNDS

Mr. MICHEL. Have you ever put together an estimate of the total amount of funds spent annually on cancer research in this country, including your program, efforts of other Federal agencies, which impact on cancer, and privately supported research endeavors?

Dr. RAUSCHER. It was almost exactly, from what we can get now, $1 billion in fiscal 1975, of which we provided $700 million, the American Cancer Society, $107 million and the rest through other Federal agencies.

Mr. MICHEL. Have funds from the American Cancer Society and these other Federal agencies increased in the last several years or been reduced?

Dr. RAUSCHER. Certainly from the American Cancer Society—their capital raising campaign went from something like $85 million 4 years ago to about $109 million this year. So, yes, it has increased.

NIH CANCER RESEARCH

Mr. MICHEL. I touched on this subject with Dr. Fredrickson yesterday, because in the overall budget presentation here, dollar wise, you are down as compared with the rest of NIH. It naturally raises all kinds of concerns. Are we turning back and away from research in the No. 1 killer, or No. 1 and 2 killers?

What can you tell us about these other institutes that contribute to cancer research within NIH, particularly those where there has been an increase this year over last, or in the budget to which you are testifying next year over this year? Are there any?

Dr. RAUSCHER. There is some very good cancer work or cancer-related work being done by some of the other institutes. Of this there is no question. I might point out about $6 million of NCI dollars are used at least in part to support that work, as a transfer from NCI into the other institutes.

Mr. MICHEL. But there must be even more cancer-related work being done by other institutes on their own appropriations.

Dr. RAUSCHER. There is no question about this. We work very closely with people in the other institutes. I think Dr. Frederickson is going to try to come up with some harder figures on this.

I think it bears repeating, however, that not only can we expect, indeed hope, that we will get information from the other institutes of benefit to cancer, but there are many, many examples whereby work done through the cancer program is of direct benefit to other diseases.

PRIORITIES

Mr. MICHEL. Now, there have been some who have charged that cancer funding has increased so rapidly in recent years that there hasn't really been enough time to set out some cancer priorities. How would you respond to those?

Dr. RAUSCHER. I would disagree very strongly. I think our priorities are about right. We have the National Cancer plan that we provide to you once every year with a 5-year framework. It has wide input from people all over the world—at least 350 scientists from this country. So it is not an NCI or big brother kind of plan. It is reflective of what people think can be done.

It has received wide input from the President's Cancer Panel and National Cancer Advisory Board. And it is on that basis, incidentally, I was strongly urged to seek as much as $948 million this year for the program. We know that we need more money and can spend it very well. We recognize also that there are many other compelling needs in health for the Federal dollar.

I think what I am saying is I am really complying with the act and your request to come in with a solid, strong, best effort kind of proposal, within a best-of-worlds kind of budget.

Mr. MICHEL. Is there a limit to what you can spend? You come up here with your figure, and our chairman has been a strong supporter of this program, as other members of the committee, so the chairman

might say, "Well, let's add another $200 million." And we play one-upmanship and someone says, "Let's put $250,000,000 in. Somebody else says, "Shucks, I will add another hundred on the floor and get my play."

You know—the sky is the limit. What can you spend? Isn't it true that if you just had unlimited resources there surely would be some rather low priority areas funded?

Dr. RAUSCHER. Absolutely. There is very definitely a limit. For instance, this year, for the first time, we did not come in for the full authorized amount as set by the health committees of the Congress. Our authorization level for this year is $1073.5 million. We did ask for $948. This is a best-of-worlds, at the present time, budget. We can do almost all of the highest priority things with this budget, we think. But we cannot do everything.

I might point out that even last year as an average we only paid 62 percent of approved grants. So we are not going beyond that point where we would be funding low priority research. In 1977, at a budget level of $688 million we would be funding no more than an average of 10 percent of approved competing grants.

PEER REVIEW

Mr. MICHEL. Now, Doctor, I am going to ask you a series of questions, and while you are here, Dr. Fredrickson, I will ask them here verbally, and they are going to be the same questions asked of every Institute in this whole area of peer review, panels, grant applications, et cetera.

No. 1—How many separate peer review panels do you have in your shop?

Dr. RAUSCHER. Thirty-six, not including study sections.

Mr. MICHEL. What is a study section?

Dr. RAUSCHER. A study section is the review mechanism in the Division of Research Grants that provides peer review for all of the grant proposals submitted to the Institutes at the NIH. There are 55 of those.

Mr. MICHEL. How many grants on the average do they review and approve in your shop?

Dr. RAUSCHER. We have about 4,000 grants and contracts funded by the NCI, and about one-fourth are contracts. So the answer to your question would be 3,000.

Mr. MICHEL. Who selects the members of these panels?

Dr. RAUSCHER. In many cases there are groups of peers that make recommendations to me, or my senior program leaders, or we solicit nominations widely throughout the scientific community.

Mr. MICHEL. My next question was going to be, where do the individuals selected come from? You have touched on that. But it is not very specific.

Dr. RAUSCHER. Most come from the academic community. There has been sort of a tradition that people come from either the academic or nonprofit research organizations. As a matter of fact, one of the criticisms that I have of myself is that I don't select enough people from

the profitmaking or taxpaying sector of the community. So it is almost always from the academic community.

Mr. MICHEL. Does that present a problem for you?

Dr. RAUSCHER. I think it presents a problem for those who are not represented on our committees, and on occasion it prevents me from getting perhaps some of the very best people in the country that may find themselves at that particular time working for a commercial organization.

Mr. MICHEL. Is just working for a commercial organization an inhibiting factor in their being ferreted out?

Dr. RAUSCHER. No, it should not be. I don't think it is. It is simply more or less traditional. There is high competition, of course, among profitmaking organizations. They do in fact make a fee on some of the work performed. And it simply has been thought in the past more or less inappropriate that they serve.

Dr. FREDRICKSON. Mr. Michel, if I might add a comment to that, it has been a rule in NIH since about 1964 that employees of profitmaking corporations not serve on grant review committees.

I believe in your instance they may on contract reviews, in certain instances.

Dr. RAUSCHER. But very few.

Mr. MICHEL. Is there any basic criteria used to govern the selection of these individuals—these peer review panels?

Dr. RAUSCHER. The basic criteria is his peer standing in the field, if you will. And you judge this by what he has done, and by the quality and number of his publications.

Mr. MICHEL. Do you have a different standard than they do over in the Heart Institute?

Dr. RAUSCHER. I don't think so.

Mr. MICHEL. Doctor, does each of the institutes have a universal pattern for criteria?

Dr. FREDRICKSON. I would say, within the realm of possibility, they are relatively uniform—certainly for all the study sections.

Mr. MICHEL. Of course, since I am going to ask this of each institute, if there are those that are standard and uniform, obviously we don't need to have it repeated. But if there is some special extenuating circumstance that we ought to know about, in your case, for example, in cancer, I do not know what that is.

Dr. RAUSCHER. I do not think so. We are after quality and expertise.

Mr. MICHEL. Do any of these individuals sit on more than one panel?

Dr. RAUSCHER. Not generally on chartered standing committees with one exception to that. A Presidentially-appointed board or panel, the President's Cancer Panel and National Cancer Advisory Board. Members of it can serve on other committees. But that is the only exception I know of.

Mr. MICHEL. What kind of reimbursement do they receive?

Dr. RAUSCHER. They receive usually $145 a day. It is the equivalent of the top civil service salary, if they qualify for that, in terms of

their peer standing. And they receive their travel compensation. Some of these people don't accept honoraria. They simply accept their expenses.

Mr. MICHEL. I think you ought to provide for the record your most recent list of review panels, the names of the people, and the institutions they come from, who serve on each panel, and how often do they usually meet?

Dr. RAUSCHER. It depends on the committee, again. But of the order of four times a year, as an average.

Mr. MICHEL. Then let's have the dates they met, and the total number of grants they approved on those dates.

Dr. RAUSCHER. I believe you mean contracts.

Mr. MICHEL. All right.

Dr. RAUSCHER. Yes; we will provide that.

Dr. FREDERICKSON. Mr. Michel, can we ask a clarification?

Mr. MICHEL. Since you single out contracts, what is the procedure with respect to grants?

Dr. FREDERICKSON. If I might perhaps enlarge on that just a moment—all the grant applications that come into the NIH are reviewed by a set corps of study sections, for all the institutes. After a scientific merit review, the applications are then distributed to the various institutes, where the work seems most appropriately to be potentially funded.

So, NIH centrally then, establishes the procedures of the study section and directs the supplementation or the renewal of the force of people there.

The division of research grants can supply the full names and institutional identification of all people in the study sections. The names of these units are published annually by the NIH and are readily available. We certainly can supply them to you.

Contract programs, however, are reviewed by the institutes themselves. And I think that is the reason for the apparent dichotomy here in the answer to your question.

Dr. RAUSCHER. We can provide you with the kind of information you asked for on all dollars going out of the NCI, but without the grants.

[The information follows:]

REVIEW GROUPS OF NCI

The following is a list of all review groups of the National Cancer Institute in fiscal year 1975 which reviewed grant or contract applications. It is important to note that the list does not include those review groups (such as the President's Cancer Panel) which meet to give scientific advice and program guidance to the national cancer program but do not review specific grant or contract applications. The number of applications reviewed and approved by the National Cancer Advisory Board is not given as the function of the Board is to provide a secondary rather than primary review. All grant applications in excess of $35,000 total direct costs annually, must receive the approval of the Board before a grant award can be made.

REVIEW GROUPS OF NCI

Committee: Members/institution	Meeting date	Grant/contract applications	
		Reviewed	Approved
Advisory Group on Vaginal Cytology—Ad hoc (contracts): Dr Sidney Aerj, American Cancer Society; Mrs. William M. Blair, public representative; Dr. Ralph Buncher, University of Cincinnati; Dr. Saul Gusberg, Mount Sinai Medical School; Mrs. Robert W. Huff, public representative; Mrs. William Johnson, public representative; Dr. Eileen King, University of California at San Francisco; Dr. Leopold Koss, Albert Einstein Medical Center; Dr. Seymour Romney, Albert Einstein Medical Center; Dr. Charles Schwinn, private physician; Dr. Elizabeth Stern, University of California at Los Angeles; Dr. Brian Henderson, University of Southern California; Dr. Kenneth Olson, National Cancer Institute.	April 1, 1975	9	0
Baltimore Cancer Research Center Review Committee—Ad hoc (contracts): Dr. Richard Warbasse, PHS Hospital Baltimore; NCI staff.	Sept. 6, 1974	15	9
	Feb. 14, 1975	1	1
	May 27, 1975	2	2
Biometry and Epidemiology Contract Review Committee (contracts): Dr. William Haenszel, National Cancer Institute; Dr. Leonard Chiazze, Jr., Georgetown University; Dr Flossie Cohen, Wayne State University; Dr. Janet Elashoff, Center for the Advanced Studies in the Behavioral Sciences; Dr. Charles Key, University of New Mexico; Dr. Sidney Marks, Energy Research and Development Administration; Dr. Anna Meadows, Children's Hospital of Philadelphia; Dr. Raymond Seltser, Johns Hopkins University.	Sept 11, 1974	11	10
	Jan. 7–8, 1975	5	5
	Apr. 8–9, 1975	12	10
Breast Cancer Diagnosis Committee (contracts): Dr. William Pomerance, National Cancer Institute; Dr. Eugene DeSombre, University of Chicago; Dr Harvey Geller, National Cancer Institute; Dr K. Robert McIntire, National Cancer Institute; Dr. Guy Robbins, Cornell University; Dr. Peter Rosen, Memorial Hospital for Cancer and Allied Diseases; Dr. Philip Strax, Guttman Institute; Dr. William Taylor, Mayo Clinic.	Sept. 11–12, 1974	4	0
	Nov. 7, 1974	12	3
	Mar. 21, 1975	15	8
Breast Cancer Epidemiology Committee (contracts): Dr. Gregory O'Conor, National Cancer Institute; Dr. Pelayo Correa, Louisiana State University; Dr. William Haenszel, National Cancer Institute; Dr. Marvin Kirschner, New Jersey Medical School; Dr. Willian London, Institute for Cancer Research; Dr. Anthony Miller, National Cancer Institute of Canada; Dr. Alan Morrison, Harvard University; Dr. Edmund Murphy, Johns Hopkins University; Dr. Nicholas Petrakis, University of California at San Francisco	Nov. 21, 1974	29	6
	Feb. 11, 1975	2	0
	Mar. 14, 1975	10	8
	June 13, 1975	0	0
Breast Cancer Experimental Biology Committee (contracts): Dr. Yale Topper, National Institute of Arthritis, Metabolism and Digestive Diseases Dr. Philip Bondy, Yale University; Dr. G. Roger Chalkley, University of Iowa; Dr. Lyle Dethlefsen, University of Utah; Dr Henry Freisen, University of Manitoba; Dr. Mary Glick, University of Pennsylvania; Dr. Theodore Hauschka, Roswell Park; Dr. Bernard Kaufman, Duke University; Dr. Gerald Mueller, University of Wisconsin; Dr. Satyabrata Nandi, University of California at Berkeley; Dr. Evelyn Rivera, Michigan State University; Dr. Jeffrey Schlom, National Cancer Institute.	Sept. 18–20, 1974	11	3
	Feb 10, 1975	1	0
	Apr. 3–4, 1975	15	14
Breast Cancer Treatment Committee (contracts): Dr. Paul Carbone, National Cancer Institute; Mrs. William Blair, public representative; Dr. David Byar, National Cancer Institute; Dr. Robert Cooper, University of Rochester; Dr. William Donegan, Medical College of Wisconsin; Dr. George Escher, Yeshiva University; Dr. William McGuire, University of Texas; Dr. William Payne, Mayo Clinic; Dr. Olof Pearson, Case Western Reserve University; Dr Douglass Tormey, National Cancer Institute; Dr. Samuel Wells, Duke University.	July 17, 1974	3	1
	Nov, 15, 1974	14	9
	Apr. 4, 1975	10	8
Cancer Clinical Investigation Review Committee (grants): Dr. Guilio D'Angio, Memorial Sloan-Kettering Cancer Center; Dr. Stefhen Carter, National Cancer Institute; Dr. Keewhan Choi, Georgia State University; Dr. William Creasey, Yale University; Dr. Jerome DeCossee, Medical College of Wisconsin; Dr. Rose Ellison, E. S. Meyer Memorial Hospital; Dr. Stephen Jones, University of Arizona; Dr. Audrey Evans, Children's Hospital of Philadelphia; Dr. Arvin Glicksman, Rhode Island Hospital; Dr. Theodor Grage, University of Minnesota; Dr. John Horton, Union University; Dr. Montague Lane, Baylor College; Dr. Howard Lessner, University of Miami; Dr William Levin, University of Texas; Dr. Alvin Mauer, St. Jude Children's Research Hospital; Dr. Carol Newton, University of California at Los Angeles; Dr. Nell Sedransk, State University of New York; Dr. Teresa Vietti, Washington University.	Sept. 23–25, 1974	70	58
	Jan. 20–22, 1975	53	40
	Apr. 21–23, 1975	32	7
	May 22–24, 1975	0	0
Cancer Control Community Activities Review Committee (contracts): Dr. Varoutan Chalian, Indiana University; Dr. Janet Cuttner, City University of New York; Dr. John Goldschmidt, Thomas Jefferson University; Ms. Florence Wykoff, public representative.	Mar. 6–7, 1975	32	23
	Apr. 17, 1975	4	2
	Apr. 28–28, 1975	23	9
Cancer Control Grant Review Committee (grants): Dr. Timothy Talbot, Institute for Cancer Research; Dr John Bonica, University of Washington; Dr. Patrick Cavanaugh, Duke University; Dr. Alfred Frechette, Sidney Farber Cancer Center; Dr. Thomas George, Temple University; Dr. Edward Hassinger, University of Missouri; Dr. Wolff Kirsch, University of Colorado; Dr Eleanor Lambertsen, Cornell University; Dr. William Markel, American Cancer Society; Dr. Albert Moraczewski, Pope John XXIII Medical-Moral Research and Education Center; Dr. Hugh Shingleton, University of Alabama; Dr. Charles Smart, Latter-Day Saints Hospital; Dr. Charles Spurr, Wake Forest University; Dr Elizabeth Stern, University of California at Los Angeles.	Dec. 13, 1974	0	0
	Jan. 13–14, 1975	59	8
	Feb. 27, 1975	27	11
	May 6–7, 1975	34	10

REVIEW GROUPS OF NCI—Continued

Committee: Members/institutions	Meeting dates	Grant/contract applications	
		Reviewed	Approved
Cancer Control Intervention Programs Review Committee (contracts): Dr Renilda Hilkemeyer, M.D. Anderson Hospital; Dr. William Christopherson, University of Louisville; Dr. Edward Hammond, American Cancer Society; Dr. Charles Huguley, Emory University; Dr. Robert Kagan, Southern California Permanete Medical Group; Dr. Diane Komp, University of Virginia; Dr. Paul Kotin, Temple University; Mr. Raymond Nesbit, American Cancer Society; Dr. Gadson Tarleton, Meharry Medical College; Dr. Alonzo Yerby, Harvard University.	Jan. 23–24, 1975	41	16
	Feb. 18, 1975	19	8
	Mar. 10–11, 1975	32	20
	Apr. 1, 1975	16	10
	Apr. 21–22, 1975	34	20
	May 14, 1975	21	14
	May 30, 1975	17	9
	June 17, 1975	1	1
Cancer Control Supportive Services Review Committee (contracts): Dr. Mary Arnold, Pennsylvania State University; Dr. J. Bradley Aust, University of Texas; Dr. Anne Carter, State University of New York; Dr. Ralph Engle, Cornell University; Dr. William Griffths, University of California at Berkeley; Dr. Jean Haar, State University of New York; Dr. Walter James, American Cancer Society; Dr. Isidro Martinez, Department of Health, Puerto Rico; Dr. Mark Nesbit, University of Minnesota; Dr. John Spratt, Cancer Research Center, Columbia, Mo.; Dr. Virginia Wang, University of Maryland; Dr. Jack White, Howard University.	Jan. 16–17, 1975	42	31
	Mar. 6, 1975	21	17
	Apr. 10–11, 1975	27	20
	May 12, 1975	7	4
Cancer Institutional Fellowship Review Committee—Ad hoc (grants): Dr. Robert Bast, Jr., National Cancer Institute; Dr. Gerhard Brand, University of Minnesota; Dr. Edward Bresnick, Medical College of Georgia; Dr. Harris Busch, Baylor College of Medicine; Dr. Joseph Castro, Mt. Zion Hospital and Medical Center; Dr. Robert Coon, University of Maine; Dr. Mary Curnen, Columbia University; Dr. Raymond Erikson, University of Colorado School of Medicine; Dr. Ediz Ezidinli, Mt. Sinai Hospital; Dr. Edward Gillette, Colorado State University; Dr. Allan Granoff, St. Jude's Childrens Research Hospital; Dr. Ervin Hawrylewicz, Mercy Hospital and Medical Center; Dr. Albert Kaplan, Vanderbilt University; Dr. John Keana, University of Oregon; Dr. Lawrence Lanzl, University of Chicago; Dr. John Laughlin, Memorial Sloan-Kettering Cancer Center; Dr. Paul Lauterbur, State University of New York at Stony Brook; Dr. Alexander Lawton III, University of Alabama School of Medicine; Dr. Sam Lesher, Allegheny General Hospital; Dr. Robert MacLeod, University of Virginia School of Medicine; Dr. Genevieve Matanoski, Johns Hopkins University; Dr. George Omura, University of Alabama; Dr. Peter Ove, University of Pittsburgh; Dr. Robert Parks, Brown University; Dr. Wayne Rundles, Duke University Medical Center; Dr. Marvin Siperstein, University of California at San Francisco; Dr. Ronald St. Pierre, Ohio State University School of Medicine; Dr. Charles Spurr, Wake Forest University; Dr. Robert Taub, Mt. Sinai School of Medicine; Dr. Sei Tokuda, University of New Mexico School of Medicine; Dr. Darcy Wilson, University of Pennsylvania School of Medicine; Dr. Milton Yatvin, University of Wisconsin; Dr. Lemone Yielding, University of Alabama.	May 13–17, 1975	165	136
Cancer Researh Center Review Committee (grants): Dr. Lowell Orbison, University of Rochester Cancer Research Center; Mr Joseph Boyd, University of Texas; Dr. John Brewer, Northwestern University; Mr. Charles Burbridge, Health Associates International, Inc.; Dr John Durant, University of Alabama; Dr. Harry Eagle, Yeshiva University; Dr. Saxon Graham, State University of New York; Dr. Earle Gregg, Case Western Reserve University; Dr. Dan Hightower, Texas A & M University; Dr Bart Hoogstraten, University of Kansas; Dr. Robert Kallman, Stanford University; Dr. Beatrice Lampkin, Children's Hospital Research Foundation; Dr. Max Lang, Pennsylvania State University Medical Center; Dr. Enrico Mihich, Roswell Park Memorial Institute; Dr. Mildred Phillips, State University of New York; Dr. Jesse Steinfeld, Mayo Medical School; Dr Charlotte Tan, Memorial Sloan-Kettering Cancer Center; Dr. Charles Todd, City of Hope Medical Center; Dr. David S. Yohn, Ohio State University.	Oct. 11–12, 1974	29	21
	Feb. 7–8, 1975	24	12
	May 16–17, 1975	16	14
Cancer Review Committee for a Cancer Center Program—Ad hoc (contracts): Dr. Lester Breslow, University of California at Los Angeles; Dr. Robert Elliott, Denver Regional Cancer Center; Dr Robert Johnson, University of Wisconsin; Dr. James Nickson, University of Tennessee; Dr. Alfred Popma, Mountain States Tumor Institute; Dr. George Santos, Johns Hopkins University; Dr. Jack Hoak, University of Iowa Hospitals.	Dec. 17, 1974	1	1
Cancer Special Program Advisory Committee (grants): Dr. Jan Steiner, University of Toronto; Dr Renato Baserga, Temple University; Dr. Tamar-Ben-Porat, Vanderbilt University; Dr. George Bryan, University of Wisconsin; Dr. Walter Gilbert, Harvard University; Dr. Vincen Hollander, Hospital for Joint Diseases and Medical Center; Dr. Charles Irving, Veterans, Administration Hospital; Dr. George Mandel, George Washington University; Dr. Albert Owens, Jr., Johns Hopkins University; Dr. Frederick Philips, Sloan-Kettering Institute for Cancer Research; Dr. Noel Rose, Wayne State University; Dr. Leonard Warren, University of Pennsylvania.	Oct. 18–19, 1974	10	9
	Feb. 6–7, 1975	8	6
	May 15–16, 1975	17	11
Carcinogenesis Program Scientific Review Committee A (contracts): Dr. Howard Bern, University of California; Dr. Peter Goldman, Harvard University; Dr. Robert Palmer, Rockefeller University.	Apr. 21, 1975	7	7
Carcinogenesis Program Scientific Review Committee B (contracts): Dr. James Flesher, University of Kentucky; Dr. Adele Kostellow, Yeshiva University; Dr. Prabhakar Lotlikar, Temple Univeristy; Dr. Paul Talalay, Johns Hopkins University; Dr. Floie Vane, Hoffmann-La Roche, Inc.; Dr. Nien-Chu Yang, University of Chicago.	Apr. 21, 1975	3	3

REVIEW GROUPS OF NCI—Continued

Committee: Members/institutions	Meeting dates	Grant/contract applications	
		Reviewed	Approved
Carcinogenesis Program Scientific Review Committee (contracts): Dr. Gerald Bartlett, Pennsylvania State University; Dr. Robert Dougherty, State University of New York Upstate Medical Center; Dr. Veronica Maher, Michigan Cancer Foundation; Dr Andrew Sivak, Arthur D. Little, Inc.	Apr. 21, 1975	4	3
Clinical Cancer Education Committee (grants): Dr. Laird Myers, Memorial Sloan-Kettering Cancer Center; Dr Margaret Abernathy, Georgetown University; Dr. Harry Bisel, Mayo Clinic; Dr. Marvin Block, University of North Carolina; Dr. Tapas Das Gupta, University of Illinois; Dr. Raymond Hall, Kansas City College of Osteopathic Medicine; Dr. Louis Hansen, University of California at San Francisco; Dr. Barbara Jones, West Virginia University; Dr. Victor Marcial, University of Puerto Rico Medical Sciences Campus; Dr. Katherne Massey, Meharry Medical College; Dr. Mary Matthews, Veterans' Administration Hospital; Dr. Susan Mellettee, Medical College of Virginia; Dr. Herbert Millard, University of Michigan; Dr. Edwin Mirand, Roswell Park Memorial Institute; Dr. Robert Nesbitt, State University of New York Upstate Medical Center; Dr. Janet Parker, Medical College of Pennsylvania; Dr. Frederick Peagler, Howard University; Dr. Gene Ridenhour, Ellis Fischel State Cancer Hospital; Dr. Harlan Spjut, St. Luke's Episcopal Hospital; Dr. Miles Standish, Indiana University; Dr. Hilde Tillman, New England Medical Center; Dr. Blanche Urey, University of Florida; Dr. Alexander Walt, Wayne State University.	Feb. 6, 1975 Apr. 30–May 1, 1975.	50 10	45 8
Clinical Oncology Committee–Ad hoc (contracts): NCI staff	Aug. 12, 1974 Oct. 4, 1974 Feb. 10, 1975 Apr. 1, 1975 May 14, 1975 June 4, 1975	18 11 12 16 14 1	16 9 9 14 13 1
Committee on Cancer Immunobiology (contracts): Dr. William Terry, National Cancer Institute; Dr. Bernard Amos, Duke University; Dr. Michael Edidin, Johns Hopkins University; Dr. Claudia Henry, University of California at Berkeley; Dr. Rosalind Kornfeld, Washington University; Dr. Stanley Mathenson, Yeshiva University; Dr. Michael Potter, National Cancer Institute; Dr. Richmond Prehn, Institute for Cancer Research; Dr. David Sachs, National Cancer Institute; Dr. Willys Silvers, University of Pennsylvania; Dr. Henry Winn, Massachusetts General Hospital; Dr. John Wunderlich, National Cancer Institute.	Sept. 30, 1974 [1] Dec. 23, 1974 [1] Feb. 24, 1975 [1] Mar. 5–6, 1975 Mar. 31, 1975 [1] Apr. 28, 1975 [1] May 19–20, 1975 June 26, 1975 [1]	4 8 5 137 8 5 3 2	0 21 6 1 3 2
Committee on Cancer Immunodiagnosis (contracts): Dr. Ronald Herberman, National Cancer Institute; Dr. Claude Arnaud, Mayo Clinic; Dr. Tibor Borsos, National Cancer Institute; Dr. Gloria Heppner, Brown University; Dr. Yashar Hirshaut, Memorial Hospital for Cancer and Allied Diseases; Dr. Thomas Mack, University of Southern California; Dr. Donald Marcus, Yeshiva University; Dr. Robert McIntire, National Cancer Institute; Dr. Victor Mussenzweig, New York University; Dr. Ralph A. Reisfeld, Scripps Clinic and Research Foundation; Dr. Gustavo Reynoso, Wilson Memorial Hospital; Dr. Ross Rocklin, Harvard University; Dr. Stuart Schlossman, Sidney Farber Cancer Center; Dr. Daniel Thor, University of Texas· Dr. Thomas Waldmann, National Cancer Institute; Dr. Ralph Williams, Jr., University of New Mexico.	[1] Sept. 10, 1974 [1] Nov. 8, 1974 [1] Jan. 7, 1975 Mar. 9–10, 1975 June 16–17, 1975	3 2 4 49 3	2 2 3 11 2
Committee on Cancer Immunotherapy (contracts): Dr. William Terry, National Cancer Institute; Dr. Julius Bekesi, Mount Sinai School of Medicine; Dr. Avrum Bluming, New England Medical Center Hospital; Dr. Christopher Benney, Johns Hopkins University; Dr. Evan Hersh, University of Texas; Dr. O. Ross McIntyre, Dartmouth College; Dr. Charles Moertel, Mayo Medical School; Dr. Steven Rosenberg, National Cancer Institute; Dr. Paul Russell, Harvard University; Dr. Sydney Salmon, University of Arizona; Dr. Richard Smith, University of Florida; Dr. Osias Stutman; Memorial Sloan-Kettering Institute for Cancer Research.	[1] Oct. 10, 1974 [1] Nov. 7, 1974 [1] Dec. 12, 1974 Jan. 9, 1975 Feb. 26–28, 1975 [1] Mar. 20, 1975 [1] Apr. 10, 1975 Apr. 24, 1975 May 29–30, 1975	1 1 4 2 70 4 5 3 4	1 1 4 2 13 3 2 3 3
Committee on Cytology Automation (contracts): Dr. Chester Herman, National Cancer Institute; Dr. Eileen King, University of California at San Francisco; Dr. Lewis Lipkin, National Cancer Institute; Dr. Richard Malmgren, George Washington University; Dr. Myron Melamed, Memorial Hospital for Cancer and Allied Diseases; Dr. Paul Mullaney, University of California at Los Alamos; Dr. Stanley Patten, Jr., University of Rochester, Dr. Judith Prewitt, National Institute of Health; Dr. William Siri, University of California at Berkeley; Dr. William Wattenburg, Comprehensive Health Services, Inc.; Dr. George Wied, University of Chicago.	Sep. 18–19, 1974 Jan. 23, 1975	5 8	1 6
Diagnostic Radiology (contracts): Dr. William Pomerance, National Cancer Institute; Dr. James Adelstein, Harvard University; Dr. Jo Ann Haberman, University of Oklahoma; Dr. David Kuhl, University of Pennsylvania; Dr. Patricia McIntyre, Johns Hopkins University; Dr. Judith Prewitt, National Institute of Health; Dr. Richard Rifkind, Columbia University; Dr. Paul Sherlock, Memorial Sloan-Kettering Cancer Center; Dr. Max Woodbury, Duke University.	Oct. 31–Nov. 1, 1974. Dec. 19, 1974 Apr. 23, 1975	48 7 9	6 2 1
Diagnostic Research Advisory Group (contracts): Dr. William Pomerance, National Cancer Institute; Dr. John Berg, University of Iowa; Dr. John Doppman, National Institutes of Health; Dr. Vay Liang Go, Mayo Medical School; Dr. Ronald Herberman, National Cancer Institute; Dr. Alfred Ketcham, University of Miami; Dr. Richard Lester, Duke University; Dr. William Odell, Harbor General Hospital; Dr. Kenneth Olson, National Cancer Institute; Dr. Marvin Schneiderman, National Cancer Institute; Dr. Alton Sutnick, Institute for Cancer Research; Dr. Louis Wasserman, Mount Sinai School of Medicine.	Sept. 12, 1974 Oct. 15–16, 1974 Dec. 12, 1974 Apr. 29, 1975	0 17 29 5	0 5 7 5

REVIEW GROUPS OF NCI—Continued

Committee: Members/institutions	Meeting dates	Grant/contract applications	
		Reviewed	Approved
Drug Research and Development Review Committee—Ad hoc (contracts): NCI staff.	Aug. 23, 1974	1	1
	Sept. 19, 1974	1	1
	Oct. 10, 1974	4	4
	Nov. 14, 1974	4	4
	Dec. 5, 1974	2	2
	Jan. 10, 1975	4	4
	Jan. 29, 1975	3	3
	Mar. 13, 1975	3	3
	Apr. 10, 1975	7	7
	May 15, 1975	6	6
	June 11, 1975	2	2
Experimental Therapeutics Committee—Ad hoc (contracts): NCI staff	July 14, 1974	3	2
	Aug. 28, 1974	5	3
	Sept. 25, 1974	3	1
	Nov. 14, 1974	5	3
	Nov. 25, 1974	3	2
	Jan. 23, 1975	3	1
	Feb. 4, 1975	4	2
	Mar. 12, 1975	3	1
	Apr. 3, 1975	3	1
	Apr. 4, 1975	4	2
	Apr. 11, 1975	4	2
	May 2, 1975	4	2
	May 5, 1975	3	2
	May 7, 1975	3	2
	May 13, 1975	5	3
Molecular Control Working Group (grants): Dr. Ernest Borek, University of Colorado; Dr. Britton Chance, University of Pennsylvania; Dr. Carolyn Cohen, Brandeis University; Dr. Josef Fried, University of Chicago; Dr. Gio Gori, National Cancer Institute; Dr. Robert Handschumacher, Yale University; Dr. Robert Holley, Salk Institute for Biological Studies; Dr. Wolfgang Joklik, Duke University; Dr. Eugene Kennedy, Harvard University; Dr. Elliott Osserman, Columbia University; Dr. Philip Stansly, National Cancer Institute.	Jan. 7, 1975	2	2
	May 28, 1975	0	0
National Bladder Cancer Project Working Cadre—Ad hoc: Dr. Gilbert Friedell, St. Vincent Hospital; Dr. William Creasey, Yale University; Dr. John Fahey, University of California at Los Angeles; Dr. George Farrow, Mayo Clinic; Dr. Thomas Hakala, VA Hospital; Dr. Charles King, Michael seese Hospital; Dr. Richard Malmgren, George Washington University; Dr. Rnthony Miller, University of Toronto; Dr. David Paulson, Duke Univer-Aty Medical Center and Veterans' Administration Hospital; Dr. Fred Riapp, Milton S. Hershey Medical Center; Dr Morris J. Wizenberg, University of Oklahoma.	Sept. 12–13, 1974	14	8
	Dec. 5–6, 1974	12	11
	Feb. 8, 1975	3	1
	Mar. 27, 1975	6	3
	June 26–27, 1975	15	8
National Cancer Advisory Board (grants): Dr. Jonathan Rhoads, Harvard University; Dr. Harold Amos, Harvard University; Dr. William Baker, Bell Telephone Laboratories, Inc.; Mr. Elmer Bobst, Warner-Lambert C .; Mr. Norris Cotton, public representative; Dr. Frank Dixon, Scripps Clinic and Research Foundation; Dr. Denman Hammond, University of Southern California; Dr. Werner Henle, Children's Hospital of Philadelphia; Dr. John Hogness, University of Washington; Mr. Donald Johnson, Advertisers Press, Inc.; Mrs. Mary Lasker, Albert and Mary Lasker Foundation; Dr. Irving London, Massachusetts Institute of Technology; Dr. Gerald Murphy, Roswell Park Memorial Institute; Dr. Joseph Ogura, Washington University; Dr. William Powers, Washington University; Mr. Laurence Rockefeller, Memorial Sloan-Kettering Cancer Center; Dr. Philippe Shubik, University of Nebraska Medical Center; Dr. Howard Skipper, Southern Research Institute ex-officio; Mr. Casper Weinberger, Secretary, Department of Health, Education. and Welfare; Dr. Ronald Lamont-Havers, National Institutes of Health; Dr. Guyford Stever, National Science Foundation; Dr. James Cowan, Department of Defense; Dr. John Chase, Veterans' Administration; Dr. Edward Burger, Jr., U.S. National Science Foundation; Dr. James Hansen, Armed Forces Institute of Pathology; Dr. Lyndon Lee, Jr., Veterans' Administration.	Oct. 7–9, 1974		
	Nov. 18–20, 1974		
	Mar. 17–18, 1975		
	June 16–18, 1975		
National Large Bowel Cancer Project Working Cadre—Ad hoc (grants): Dr. Rulon Rawson, M.D. Anderson Hospital and Tumor Institute; Dr. Renato Baserga, Fels Research Institute; Dr. Gerald Dodd, University of Texas; Dr. Emil Freireich, M.D. Anderson Hospital and Tumor Institute; Mr. William Haenszel, National Cancer Institute; Dr. Kurt Isselbacher, Harvard Medical School; Dr. Martin Lipkin, Sloan-Kettering Institute Memorial Hospital; Dr. Charles McKhann, University of Minnesota Hospital; Dr. Victor A. McKusick, Johns Hopkins Hospital; Dr. Antolin Raventos, University of California at Davis School of Medicine; Dr. Alan Sartorelli, Yale University School of Medicine; Dr. Paul Sherlock, Memorial Sloan-Kettering Cancer Center; Dr. William Shingleton, Duke University Medical Center; Dr. Charles Todd, City of Hope Medical Center; Dr. Lee Wattenberg, University of Minnesota School of Medicine; Dr. John Weisburger, American Health Foundation; Dr. David Wood, University of California at San Francisco.	Sept. 6, 1974	17	9
	Jan. 22, 1975	19	10
	Mar. 25, 1975	16	11
	June 20, 1975	12	7

REVIEW GROUPS OF NCI—Continued

Committee: Members/institutions	Meeting dates	Grant/contract applications	
		Reviewed	Approved
National Pancreatic Cancer Project Working Cadre—Ad hoc (grants): Dr. Isidore Cohn, Jr., Louisiana State University School of Medicine; Dr. W. Anderson, University of Miami School of Medicine; Dr. Rogert Connelly, National Cancer Institute; Dr. Douglas Holyoke, Roswell Park Memorial Institute; Dr. James Jamieson, Yale University School of Medicine; Dr. Richard McHugh, University of Minnesota; Dr. Lee Roy Morgan, Jr., Louisiana State University School of Medicine; Dr. H. M. Pollard, University of Michigan Medical School; Dr. Josef Rosch, University of Oregon Health Sciences Center; Dr. Philip Schein, Georgetown University Hospital; Dr. Paul D. Webster III, Medical College of Georgia; Dr. Norman Zamcheck, Boston City Hospital.	Apr. 30, 1975	2	1
National Prostatic Cancer Project Working Cadre—Ad hoc (grants): Dr. Gerald Murphy, Roswell Park Memorial Institute; Dr. Malcolm Bagshaw, Stanford University; Dr. David Byar, National Cancer Institute; Dr. Donald Coffey, Johns Hopkins Hospital; Dr. Robert Gaunt, Ciba-Geigy Corp.; Dr. Ruben F. Gittes, University Hospital; Dr. Harry Handelsman, National Cancer Institute; Dr. John Horton, Albany Medical College of Union University; Dr. George Hutchison, Harvard School of Public Health; Dr. Gerald Johnston, National Institutes of Health; Dr. Jack Saroff, Roswell Park Memorial Institute; Dr. Donald Merchant, Eastern Virginia Medical School; Dr. Rathollah Mostofi, Armed Forces Institute of Pathology; Dr. Richard Pledger, National Cancer Institute; Dr. Noel Rose, Wayne State University; Dr. Betty Rosoff, Yeshiva University; Dr. William Scott, Johns Hopkins University; Dr. Michael Sigel, University of Miami; Dr. Pentii Siiteri, University of California at San Francisco.	July 23–24, 1974 Nov. 12, 1974 Feb. 4, 1975 May 13, 1975 June 12–13, 1975	3 5 8 12 4	2 3 3 8 2
Surce Evaluation Groups—Ad hoc (contracts): NCI/NIH staff	July, 1974 Aug. 6, 1974 Aug. 22, 1974 Nov. 7, 1974 Nov. 26, 1974 Dec. 10, 1974 Dec. 16, 1974 Dec. 20, 1974 Jan. 14, 1975 Jan. 23, 1975 Jan. 27, 1975 Feb. 7, 1975 Feb. 19, 1975 Mar. 12, 1975 Mar. 17, 1975 May 1, 1975 May 15, 1975	2 2 8 7 12 14 4 29 6 3 12 4 3 4 13 3 13	1 1 2 2 4 5 1 9 2 1 4 1 1 1 4 1 3
Review Group on Breast Cancer Treatment—Ad hoc (contracts): Mrs. William Blair, Jr., public representative; Dr. David Bayer, National Cancer Institute; Dr. Michael Brennan, Michigan Cancer Foundation; Dr. Paul Carbone, National Cancer Institute; Dr. Robert Cooper, Jr., University of Rochester Cancer Center; Dr. Marvin Kirschner, Newark Beth Israel Hospital; Dr. William McGuire, University of Texas Medical School; Dr. William Meakin, Ontario Cancer Institute; Dr. David Page, Vanderbilt University; Dr. William Payne, Mayo Clinic; Dr. Olof Pearson, Case Western Reserve University; Dr. John Schilling, University of Washington; Dr. Russell Sherwin, University of Southern California; Dr. J. Robert Stewart, University of Utah; Dr. Douglass Tormey, National Cancer Institute.	Feb. 9, 1975	9	1
Review Committee for Frederick Cancer Research Center—Ad hoc (contracts): Dr. Chester Alper, Harvard Medical School; Dr. Dani Bolognesi, Duke University; Dr. Amiel Cooper, Tufts University; Dr. Maurice Hilleman, Merck Institute for Therapeutic Research; Dr. Benjamin Papermaster, Boston University Medical School; Dr. Hugues Ryser, Boston University Medical School; Dr. James Liverman, Energy Research Development Agency.	Jan. 8, 1975	1	1
Virus Cancer Program Scientific Review Committee A (contracts): Dr. Marcel Baluda, University of California at Los Angeles; Dr. David Bishop, Rutgers University; Dr. Arthur Brown, University of Tennessee; Dr. Donald Fine, Litton Bionetics, Inc.; Dr. Raymond Gilden, Flow Laboratories, Inc.; Dr. Eva Klein, Karolinska Institute; Dr. Mathilde Krim, Sloan-Kettering Institute for Cancer Research; Dr. Arleen Levin, Rush-Presbyterian-St. Luke's Medical Center; Dr. Miriam Lieberman, Stanford University; Dr. Frank Lilly, Yeshiva University; Dr. Hans Meier, Jackson Laboratory; Dr. William Moloney, Peter Bent Brigham Hospital; Dr. Richard Morrow, Harvard University; Dr. Malcolm Pike, University of Southern California; Dr. William Rawls, McMaster University; Dr. Kirby Smith, St. Jude Children's Research Hospital; Dr. Kenneth Takemoto, National Institute of Allergy and Infectious Diseases; Dr. Lise Thiry, Institut Pasteur.	Oct. 2, 1974 Nov. 8, 1974 Nov. 10, 1974 Feb. 9, 1975 Feb. 13, 1975 Apr. 10, 1975 Apr. 18, 1975 Apr. 24–27, 1975 May 16, 1975	1 6 2 3 4 7 6 6 5	1 5 2 3 4 7 5 5 5

REVIEW GROUPS OF NCI—Continued

Committee: Members/institutions	Meeting dates	Grant/contract applications	
		Reviewed	Approved
Virus Cancer Program Scientific Review Committee B (contracts): Dr. J. Thomas August, Yeshiva University; Dr. Paul Black, Massachusetts General Hospital; Dr. Dani Bolognesi, Duke University; Dr. Janet Butel, Baylor College of Medicine; Dr. Robert Chanock, National Institute of Allergy and Infectious Diseases; Dr. Joseph Feldman, Scripps Clinic and Research Foundation; Dr. Clarence Gibbs, Jr., National Institute of Neurological Diseases and Stroke; Dr. Adeline Hackett, University of California at Berkeley; Dr. Francoise Haguenau, College De France; Dr. Janet Hartley, National Institute of Allergy and Infectious Diseases; Dr. Gertrude Henle, Children's Hospital of Philadelphia; Dr. Jacob Holper, Litton Bionetics, Inc.; Dr. Edmund Klein, Roswell Park Memorial Institute; Dr. Henry Lynch, Creighton University; Dr. Paul Weiman, University of Washington; Dr. Marvin A. Rich, Michigan Cancer Foundation.	July 22, 1974	2	3
	Nov. 10, 1974	4	3
	Nov. 14, 1974	3	7
	Feb. 26–27, 1975	8	4
	Apr. 28, 1975	4	

[1] Conference calls.

Mr. MICHEL. Is it possible for a member of a peer review group to receive a research grant or contract from your institute?

Dr. RAUSCHER. Yes, indeed, it is possible. People on study sections, as well as other peer review groups, on occasion do.

Mr. MICHEL. And do they participate in the grant proposals submitted by others from their own institution?

Dr. RAUSCHER. No, they must leave the room. This includes the councils and boards.

Mr. MICHEL. During what—just during the vote?

Dr. RAUSCHER. During discussion—during any discussion of an application from a member of their home institution.

Mr. MICHEL. What would the total cost for administering the peer review system in your institute be?

Could that be determined?

Dr. RAUSCHER. Yes, I can give you a figure.

Mr. MICHEL. All right.

Supply that for the record. This should include travel, per diem, consultant fees, secretarial assistance—in other words, the whole gamut of expenditures in this peer review process.

[The information follows:]

The total annual cost for peer review activities of the National Cancer Institute in fiscal year 1975 was $1,408,178.

Mr. MICHEL. And then finally, what kind of grant monitoring system do you have to insure that the intended research is being pursued and accomplished?

Dr. RAUSCHER. I can provide that.

[The information follows:]

GRANT MONITORING SYSTEM

NCI scientist administrators and grants management specialists monitor the progress and direction of grant-supported research by reviewing the annual progress reports and budget requests which are submitted by grantees each year as part of their noncompeting applications for committed support. Site visits are made to assess not only the institutions capabilities to perform the proposed research but to monitor its progress. NCI travel funds are utilized for this purpose as well as for the review and monitoring of contract activities. This staff monitoring occurs for all kinds of grants. Additional monitoring takes place in programs where it seems especially desirable. For example, in our targeted

organ site programs, committees advisory to national project directors, review annual progress reports. Similar annual reviews take place in the clinical education program. In addition, NCI staff arranges workshops in which grantees review their research accomplishments. Such workshops have been conducted annually for the targeted organ site programs. Recent workshops in immunology have encompassed both grantees and contractors. The centers program has developed a system by which members of the National Cancer Advisory Board, abetted by consultants can evaluate aspirants for recognition as comprehensive cancer centers. This system is being refined for monitoring the progress of existing and developing comprehensive centers. Peer review of competitive grant applications is, in itself, a monitoring process. The in-depth evaluation of competing applications by panels of experts includes a judgment of scientific merit, a review of progress (for renewals), and a consideration of the time that can elapse before the research should again require an in-depth critical peer review. This latter consideration results in an average of 3 years of committed support.

Mr. MICHEL. That is all, Mr. Chairman.

Mr. FLOOD. Mr. Natcher.

HOSPICE CONCEPT

Mr. NATCHER. Doctor, I have heard some discussion about the Hospice concept with regard to terminally ill cancer patients. What is this concept, Doctor?

Dr. RAUSCHER. It is a concept that began, I believe, largely in Scandinavia, although it is now being used in other parts of the world.

Essentially, it is a nonhospital, home-type, environment, in which the patient who is thought to be terminal can be made as comfortable as possible.

Often Hospices have consulting psychologists and nurses that are familiar with problems of the dying who provide support—not only to the patient, but also to the patient's family. It is far less expensive to the patient, and thereby to his family for that kind of care during the last days, or last period of illness.

Mr. NATCHER. Doctor, is this during a period of time when there is no drugs, no medication at all?

Dr. RAUSCHER. No. Medication in many cases is continued during that period of time, either for pain or for the disease itself.

Mr. NATCHER. Is the Cancer Institute supporting any of the Hospice programs that you know of?

Dr. RAUSCHER. About $1½ million, I am told by my colleague. I think we have three projects for that amount.

Mr. NATCHER. Do you see any expansion of this program in the future?

Dr. RAUSCHER. Yes; I do. But again, we do not pay even in the Hospice concept for the routine care of cancer patients. We are trying to demonstrate in this country that the Hospice concept for cancer is a good one. Once that demonstration is made, then we will withdraw our funds at a time when the practicing community will pick this up.

Mr. NATCHER. Doctor, can the patient in this category recover costs for the services rendered from insurance companies and other companies involved?

Dr. RAUSCHER. Yes: some of it. To the extent that he has continuing third party or unused third party coverage, that will pay for it. We do not pay for that.

EQUIPMENT

Mr. NATCHER. Now, Doctor, I believe you are requesting $5,375,000 for equipment for fiscal year 1977. In fiscal 1976, I believe you are

planning to spend some $5 million for equipment. That is correct, is it not?

Dr. RAUSCHER. That is correct.

Mr. NATCHER. Now, I see that you have spent about $4 million in 1975.

Dr. RAUSCHER. I believe you are right; yes.

Mr. NATCHER. Now, this $5 million was for equipment.

Dr. RAUSCHER. That is right.

Mr. NATCHER. Doctor, that, I believe, is something over $14 million in the last 3 years.

Would you agree on that figure?

Dr. RAUSCHER. Yes, sir.

Mr. NATCHER. What kind of equipment are you buying and why are you buying this equipment?

Dr. RAUSCHER. Well, as an example, there have been, and we anticipate this will continue, important improvements in diagnostic equipment. You have heard, I am sure, sir, about the EMI, the EMI Scanner, whereby we can determine with an improvement in X-ray equipment whether a person has a tumor in the brain, as an example, or a mass in the brain. This is so good, that it may very well do away with much exploratory surgery. This is very expensive equipment. We now have two of these units within the NCI.

There are all kinds of other devices that can peer into the body, if you will, that are very expensive. A linear accelerator is part of the cost that you just indicated.

Electron microscopes, equipment like that of major expense.

Mr. FLOOD. What is the cost of a linear accelerator, about?

Dr. RAUSCHER. About $200,000 now, of the type we are talking about. But the EMI scanner——

Dr. FREDERICKSON. The EMI scanner for the head and neck costs half a million, and for the total body will cost on the order of three-quarters of a million.

Mr. NATCHER. Now, Doctor, for the record, if you will, provide us a list of how you intend to spend the $5 million-plus for equipment in 1976, and also a list of the equipment you plan to purchase in 1977.

If you will place that in the record at this point.

[The information follows:]

National Cancer Institute
Equipment for 1976 & 1977
Object Class 31
(In thousands)

Type of Equipment	1976 Estimate	1977 Estimate
Environmental & Safety	130,000	250,000
(Tissue culture hoods, laminar flow hoods, chemical hoods & biocontainment equipment)		
Microscopes	332,800	502,000
Electron miscroscopes	(260,000)	(410,000)
Other	(72,800)	(92,000)
Serum & Chemical Analysis	1,143,900	1,367,000
Spectrophotometers	(473,000)	(514,000)
Scintillation counters	(291,000)	(426,000)
Gamma counters & beta counters	(182,000)	(202,000)
Other (ultrasound units, nuclear diagnostic system, etc.)	(197,900)	(225,000)
Constant Temperature Storage Environmental Chambers	187,200	287,000
(Walk-in freezers, liquid nitrogen freezers, incubators, etc.)		
Animal Equipment and Cages	702,000	725,000
Laboratory Support	323,000	539,000
Centrifuges/rotors	(103,000)	(254,000)
Water baths/fraction collectors	(6,700)	(22,000)
Ultracentrifuges	(143,000)	(183,000)
Other laboratory equipment	(70,300)	(80,000)
Mechanical Support	69,000	110,000
(Pumps, power supply, water chiller, etc.)		
Patient Care & Treatment	1,509,000	900,000
EMI scanner/accessories	(602,000)	(465,000)
Body heat suits/accessories	(130,000)	(40,000)
Linear accelerators/accessories	(685,000)	(300,000)
Other	(92,000)	(95,000)
ADP Equipment/Computer Support	150,000	200,000
(Adjunct computer systems)		
Office Furniture & Equipment	164,100	180,000
(Typewriters, desks, office machines, tables, chairs, etc.)		
Photography	129,000	140,000
(Film monitors/enlargers, dryers)		
Miscellaneous	160,000	175,000
(Replacement equipment and other equipment essential to laboratory operations)		
Total	$5,000,000	$5,375,000

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SCREENING PROGRAM

Mr. NATCHER. My Chairman asked you about breast screening programs and went into detail somewhat along this line. Can you tell the committee what other screening programs you are currently supporting?

Dr. RAUSCHER. Well, as an example, the Pap test is being used in many areas of the country, through our cancer control network.

Mr. MICHEL. Are there still only 25 percent of the women availing themselves of that test?

Mr. NATCHER. I yield. Go right ahead, Mr. Michel.

Dr. RAUSCHER. We believe now that of the women who are at risk, the low income, lower socio-economic women, about 75 to 80 percent of those in many areas of the country are now availing themselves of that technique. I mentioned 25 percent about 2 years ago, I believe, but it is greatly improved, primarily because of publicity.

Mr. MICHEL. I appreciate your yielding, Mr. Natcher.

Mr. NATCHER. Thank you, Mr. Michel.

Now, Doctor, what are the results of these screening programs? Are the results worth the investment? Do you feel they are worth the investment?

Dr. RAUSCHER. By far.

Mr. NATCHER. Without any question.

Dr. RAUSCHER. Without any question. Perhaps I might give you one other example of something relatively new. We have three projects in the country right now, and we anticipate this will expand, that have to do with sputum cytology. This is sort of a Pap test for the mouth, if you will, and may be used in combination with what is called a flexible bronchoscope examination. This is a piece of equipment developed by the Japanese.

It is very small, and can get down into the portions of the lung. It actually has a biopsy gear, sort of a knife, as well as a camera, and a light. You can actually see what you are cutting. We know that through the bronchoscope we can pick up lesions that are cancerous 5 years before that spot shows up big enough to be diagnosed on X-ray. Now, use of this instrument is a very sophisticated, time consuming, expensive kind of thing. So we do not think it is ever going to be widely applicable to the smokers of the country. But we have good reason to believe that the aberrant cells of a very small lesion are exfoliated or shed, can be coughed up into the sputum, and as with Pap tests for cervical carcinoma, can actually be seen as cancer cells in the sputum by cyto technicians. That is an indication, therefore, to the doctor to then use the bronchosope to go down and find the tumor, so that during surgery the surgeon knows where to go to work. We hope that within not too many more years we will have sputum cytology centers, urine cytology centers for bladder cancer, and fecal cytology centers for cancers of the large bowel. It is well worth it.

Mr. NATCHER. Doctor, can you give us some idea of the screening programs you plan for the future?

Dr. RAUSCHER. To repeat myself, we will continue with our Pap testing, especially in those women who have not for various reasons availed themselves of that technology. We will set up other sputum diagostic or cytology screening programs.

Mr. NATCHER. Anything other than this?

Dr. RAUSCHER. Mammograms, fecalgrams, that kind of thing. These certainly would be the most important.

Mr. NATCHER. You mentioned tobacco a few minutes ago. You know I am from Kentucky, Doctor.

Mr. PATTEN. He mentioned bourbon, too.

Mr. NATCHER. Doctor, I remember in 1964, when we had the Surgeon General before one of our committees, and that was at the time of the smoking report, as you recall. The Surgeon General was a right able man, just like you are, Doctor, and he said to us emphatically—when you burn tobacco and spinach, you get the same result.

You agree with that, don't you?

Dr. RAUSCHER. It certainly looks that way.

Mr. NATCHER. Don't you get the same result?

Dr. RAUSCHER. Yes; you do.

Mr. NATCHER. Thank you, Doctor. I know you would answer it that way. Thank you, Mr. Chairman.

SWINE FLU

Mr. PATTEN. I am always thrilled to meet my good friend from the old banks of the Raritan.

Now, no matter what you say, it is an epidemic. For instance, over the weekend, we had a fellow at Camp Dix die, they say from Swine Flu.

In World War I 20 million people had it. But to read the papers, you would think we have another epidemic like we did in 1917.

VINYL CHLORIDE

Now, on vinyl chloride, do you know how many plants I have that use vinyl chloride?

Dr. RAUSCHER. No, sir.

Mr. PATTEN. Fifty. There is nothing wrong with vinyl chloride. We have 500,000 people working in the chemical industry. I have had a lead factory in my town all my life—copper works, we have zinc. I go to these funeral parlors. I seldom see anyone die from vinyl chloride, or lead, or copper poisoning. I know what lead poisoning is. I saw it. I saw it when I was a kid 20 years old in the copper works.

But in my lifetime, that is the only case of lead poisoning I saw. I was happy to hear you say 4 percent. But it would seem to me among our industries, we are doing quite a bit of work, and always have in studying the occupational risks of the metals and the chemicals.

Dr. RAUSCHER. Some industries do very, very well.

Mr. PATTEN. In case you do not know it, Doctor, I can tell you it is big, because they can be ruined. It is like somebody opened up their mouth one Thanksgiving and said DDT and cranberries, bing-bing—all our cranberry farmers were killed—just before Thanksgiving and Christmas—absolutely irresponsible. Now, I have 500,000 people working in the chemical industry. We have a toxic substance bill coming up. I think we have 23 laws on that.

The point I make is if you mention anything—it may hurt many—like we say the exhaust of automobiles—you haven't said much about that. That EPA crowd keep giving you the automobile, the exhaust—let's abolish automobiles. Sixty-seven percent of environmental pollutants are caused by hydrocarbons. EPA, what do they know about this? Do they have animals and research?

Dr. RAUSCHER. Yes; they do some of their own testing. Not for carcinogenesis. We do virtually all of that ourselves.

Mr. PATTEN. You didn't say much about the exhausts.

Dr. RAUSCHER. It is still very bad stuff.

Mr. PATTEN. You said tobacco, alcohol, obesity. You hit me right in the middle.

CANCER ATLAS

One more thing. You publised an atlas, and you said my area around New Brunswick has the highest mortality rate from cancer in the world—1950 to 1969. You know Doctor, we have that college entrance testing group right there in Princeton. I don't want to disillusion anybody, but I think it is a crime that we judge 10 million people going into college on the basis of those college entrance exams. They don't give any psychiatric test.

This is not the basis for picking a cop or a lawyer. So that I am a little sour on the colleges escaping by using the college entrance test.

Tell me, Doctor—in all seriousness—how good is this Atlas that has my people in my area thinking they are all going to die of cancer?

They have us with highest mortality rate for rectal and bladder cancer and cancer of the ovaries. That is our New Jersey group. Tell me, are you going to stand by your Atlas? Or do you have a little comment about how it should be taken with reservations?

Dr. RAUSCHER. Mr. Patten, this is a record, really. Sort of a death indices that is carried by each State. It is actually a record of the people who have died from cancer, from different types of cancer in those areas. I might add, my hometown, or very close to it, was also one of the very highest in the country.

Mr. PATTEN. They draw maps. They take in the chairman's area. They draw maps—that is where the cancer air must come from. I mean it is the most ridiculous thing I ever saw.

Dr. RAUSCHER. Your question is a very important one. My concern is that it will so alarm people living in different areas, that they will be unable to live worry-free lives within those areas. As I said before, it is an analysis of reported death records from different parts of the country. The reason we think it is important is because it may help us help people in those States, by determining whether there are clues to cancer etiology, cancer causation. And I might point out I think it is important for the public to understand that even in those areas of the map, where it shows a relatively high concentration of certain cancers, we are talking about rates not exceeding about 200 people per 100,000. That is enough to be concerned about, of course, and people ought to be concerned. But to put the incidence of cancer in perspective with other disease, in all areas of the country, it is of that magnitude.

Mr. PATTEN. Did I send you any of the clippings?

LEAD POISONING

Dr. RAUSCHER. I believe you did. You sent me one clipping. I think we must recognize that there are some industries and some exposures that people will continue to experience because of the way we have to live, and in many cases want to live in society. But that kind of study is very important, because in knowing that a particular chemical may be bad for you, we can take steps to protect you from that

chemical, while we still use it. That is the importance of these kinds of studies.

Mr. PATTEN. I have three questions for our local paper, because they are all upset about this.

Now that we agree, can you provide any information to the subcommittee on why the mortality figures are so high in New Jersey and in urban areas?

Dr. RAUSCHER. I can provide that for the record.

[The information follows:]

MORTALITY DATA IN NEW JERSEY AND URBAN AREAS

Cancer mortality rates are high in New Jersey and in urban areas of the United States due to a number of factors. Smoking habits and industrial exposures contribute at least in part to the urban/rural differentials for many cancers. The excessive rate of bladder cancer among New Jersey men is believed to result from exposures of chemical workers to bladder carcinogens. A study has begun to estimate the magnitude of this occupational factor as well as other environmental exposures. We are pursuing the quantification of risk factors in a number of regions in the United States.

REGIONAL FACTORS AND CANCER

Mr. PATTEN. To what extent is the Institute investigating or sponsoring the investigation of these regional factors, now that you have your Atlas?

Dr. RAUSCHER. I can provide that for the record.

[The information follows:]

INVESTIGATION OF REGIONAL FACTORS

The Environmental Epidemiology Branch of the National Cancer Institute has commenced an investigation of bladder cancer in New Jersey with emphasis on assessing the relative contribution to the reported excess of this tumor from industrial (occupational), as well as, common environmental exposures. There is an ongoing investigation of lung and oral cancers in Florida, Georgia, and South Carolina in collaboration with the Center for Disease Control. Lung cancer is also under investigation in Maine. The reported excesses of bladder cancer in rural New England are being pursued. Additional site-specific investigations have been designed for oral cancer (North Carolina and Missouri), gallbladder cancer (West Virginia, Minnesota, Ohio, Michigan, Wisconsin), bladder cancer (Michigan, Wisconsin, Illinois, Iowa) and liver cancer in Texas.

COOPERATION

Mr. PATTEN. Is there good cooperation between the National Cancer Institute and the Environmental Protection Agency in the investigation of environmental causes of cancer?

Dr. RAUSCHER. I think there is excellent cooperation.

Mr. PATTEN. Whether it is tobacco or alcohol.

Dr. RAUSCHER. Yes. I will expand on this for the record.

[The information follows:]

COOPERATION BETWEEN NCI AND EPA

There is excellent cooperation between the National Cancer Institute (NCI) and the Environmental Protection Agency (EPA) with respect to coordination of activities in environmental causes of cancer. The NCI is represented by Dr. James A. Peters, Director, Division of Cancer Cause and Prevention, on the EPA Cancer Assessment Group, which is a newly formed committee responsible for internal review and policy on carcinogenesis within EPA. The chair-

man of that committee, Dr. Roy Albert (Deputy Assistant Administrator for Health and Ecological Effects, EPA) is a consultant to the National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis and will participate in the deliberations of the newly established NCI Committee to Review and Evaluate Carcinogenicity Data.

A second formal mechanism is the DHEW Committee to Coordinate Toxicology and Related Programs, where the EPA participates as official observers. This committee has been of great usefulness for program coordination. At a less formal level, there exists the Interagency Co'laborative Group on Environmental Carcinogenesis (headed by Dr. Herman Kraybill of NCI) which has had significant participation by EPA and has served the essential purpose of information exchange. Additionally, there has been and continues to be a considerable amount of ad hoc and relatively informal interaction between NCI and EPA personnel at virtually all organizational levels. The expectation is that with newly anticipated legis'ative authorities and newly promulgated regulations there will be a mutual need for even greater interchange and coordination.

DIABETES

Mr. PATTEN. And my last question: The National Cancer Institute is supposed to know more about abnormal cell growth and cell destruction than any other institute. You will accept that.

Dr. RAUSCHER. I will accept that.

Mr. PATTEN. Can you tell the subcommittee what NCI is doing in terms of cell destruction and aberration, as related to the diabetes problem?

Dr. RAUSCHER. We are doing very little in diabetes, and I think predictably so, because other institutes are covering that very well.

I think last year we funded something like 30 grants for less than $250,000 that had anything at all to do with diabetes. Most of those grants have no more than about 10 percent of their effort related to diabetes. We do very little in diabetes.

Mr. PATTEN. It is a pleasure to have had you here.

Mr. NATCHER. Mr. Obey.

Mr. OBEY. Mr. Chairman, before I get into my regular questions, I want to raise a few questions on topics already touched by other members.

I did want to get this into the record—following up on Mr. Michel's question on peer review and the possible conflict of interest of individuals appointed to these panels. Last year, in addition to the other information which Mr. Michel asked be inserted in the record. I also asked if we could have the information on exactly what the institutions which are represented by persons sitting on those panels receive in contracts from NCI. I do think the record ought to note it was so lengthy when we got it we could not put it in the record. It was 119 pages of contracts that were going to institutions that had representatives on NCI advisory committees.

A couple of things that were mentioned earlier, Dr. Rauscher, I think I asked you a year, 2 years ago, whether we did have any specific studies which showed a higher incidence of cancer and other diseases on the part of those living in highly urbanized areas. What is the story on that? Do we have any studies?

Dr. RAUSCHER. Yes; we have many epidemiological studies, Mr. Obey, that show that people living in highly industralized areas have a substantially greater cancer risk than those living in farm areas, as an example, or in rural areas.

It is becoming more complex than we thought it once was, however, due to difficulties in defining to what extent can we ascribe this to air pollution. That is becoming less clear than it was before.

It seems people living in urban areas smoke more, as an example, or they do or use other things, such as alcohol, more than people living in, let's say, less apparently contaminated air. So it may very well be sociologic factors or patterns of living that contribute more to one's cancer risk than would the contamination or pollution of the air.

COST OF POLLUTION

Mr. OBEY. When Dr. Newell was at the session on cancer in New York last year, he pointed up an issue which I think is often overlooked. We always quantify what cost is in economic terms, if we take certain measures to reduce pollution, for instance. But it is very seldom that we quantify the other end of the equation—what cost is to the economy because of the increased incidence of a great variety of diseases, what the cost is in terms of medical care for people who have higher incidences of those illnesses. Could you take a stab at telling us what the cost is to us from high levels of pollution around the country?

Dr. RAUSCHER. Many people have felt that the cost to the economy in lost wages, medical care—that kind of thing—of cancer alone, is of the order of $15 to $25 billion a year. Let's say $20 billion. I mentioned before that it is thought that environmental pollution can contribute as much as 4 to 5 percent to the worker exposed in his environment. Another 5 percent of cancer occurs because of the worker taking a pollutant home on his shoes or clothes, and thereby exposing his children and family.

And the third way that that kind of pollution contributes to cancer is pollution of the immediate greater environment in terms of air, water, and soil. So we are talking about 10 percent. And I think you will find that most epidemiologists in the world would agree with that 10 percent. It is stretching it a bit, I think. So let's say the cost to the economy is $20 billion, and if 10 percent of that is due to environmental pollution, then it would give you an order of magnitude—$2 billion in cancer alone.

Mr. OBEY. That does not include other diseases; it doesn't include, or does it, the cost of lost wages.

Dr. RAUSCHER. It does include that; yes. But it would not include emphysema, for instance, or chronic bronchitis.

Mr. OBEY. Where would we get the total for all diseases?

Dr. RAUSCHER. Can I talk to my colleagues out at NIH? Perhaps we could come up with a better figure for you.

Mr. OBEY. Okay. I would like to have that.

[The information follows:]

ECONOMIC LOSS FOR ENVIRONMENTALLY INDUCED DISEASES

The Bureau of Labor Statistics estimates the direct work compensation lost from all diseases (not accidents) was $29 billion in 1974. This figure does not include medical expenses nor income losses after death. It should be realized that much of the chronic bronchitis, emphysema, and heart disease in workers is related primarily to smoking tobacco and diet, and not to their environment per se.

The $2 billion loss estimated for work-related cancer includes medical costs and wages lost after death, but not wages lost while sick which should be relatively

small. For instance, if a 49-year-old worker earning $10,000 per year develops lung cancer and dies in 1 year, he will lose about $10,000 in work compensation and his medical expenses will be about $6,000. but he will also lose 15 years of potential income to age 65 which is equivalent to $150,000.

HEAD AND NECK SCANNER

Mr. OBEY. These head and neck scanners were mentioned a while ago. I saw one in operation just a few weeks ago. How many are now operating around the country?

Dr. FREDRICKSON. There must be several hundred, at least, Mr. Obey. I am not sure of the exact number.

Mr. OBEY. The reason I ask this question—I can recall a few years ago, I had two hospitals in my hometown, because the doctors on one end of town would not talk to the doctors at the other end—so for 20 years we had two hospitals when we should have had one.

We had machinery used a very small part of the time each year in both hospitals. What I am wondering is how much of a danger do you have with this kind of an instrument, how much of a danger you have in its being acquired simply because it is the thing to have. How many of these should we have around the country before we begin having a surplus?

Dr. FREDICKSON. You have touched upon an extraordinarily important problem—because it is not only the institutional rivalries that do exist, as you say, but doubtless, as these scanners become more available, it will be thought necessary to submit nearly every patient with a complaint of headache to this kind of scan because there will be occasions when it will reveal things you cannot see in any other way. At the very least, there is going to have to be some collective responsibility, at the level of the communities, for providing this service.

Perhaps there will have to be more than that in regard to the health planning agencies and their interaction in regard to buying such large capital equipment.

At the very least, it also means those who have these units will have to run them at a maximum. Some of the units now available at the NIH, for example, are running 12 to 16 hours a day, to take maximum advantage of them.

This is a big problem. There is no obvious and immediate solution to it. But I think we are aware of it in the medical community.

Dr. NEWELL. May I add one thing, Mr. Obey? There is a meeting scheduled April 25 to the 27th, in St. Louis, sponsored by the American College of Radiology, which will bring together the experts in computerized diagnostic procedures, and it will in fact be a policy meeting as well as a State-of-the-art-meeting. And this item is on the agenda.

OCCUPATIONAL CARCINOGENESIS

Mr. OBEY. I wonder if you could enlighten me on one point. You mentioned 4 percent at one point in the hearing, and then you mentioned 10 percent. I am trying to untangle those two figures.

Dr. RAUSCHER. All right. We are talking about the effects of occupational carcinogenesis, really. It can be broken down into three categories. Let's say 5 percent of cancers are attributable to direct exposure of the worker at the work place. That is 5 percent. Then the other 5 percent breaks down into two categories.

The first is the effects of the worker—the contaminated worker carrying such things perhaps as kepone, or pesticide, or a chemical home on his clothes, in which case his family is exposed. And the third part of that is immediate contamination of water, soil and air right around the factory, or right around the city in which that major polluting factory, let's say, may be located. And my epidemiology people, as well as those of the World Health Organization, tell me that about 10 percent of our cancers are attributable to occupationally induced cancers in those three categories.

Mr. OBEY. How do you arrive at an estimate like that? How do you make one, given what you mentioned earlier, that there is so much that we simply don't know?

Dr. RAUSCHER. Well, primarily from actual records of people who have developed occupation-related cancers and to some extent, as a projection of specific cancers that occur predominantly in a small geographic area.

Mr. OBEY. Let me ask, for for instance—when we talked about vinyl chloride earlier, it is my understanding that the vinyl chloride problem was first discovered because you had a high incidence of angiosarcoma. It is my understanding after those records were reviewed, they discovered not only did you have higher incidence of angiosarcoma, but you also had higher incidence of lung cancer and others as well.

Dr. RAUSCHER. I certainly know about angiosarcoma. But when you say high incidence, I believe I am right when I say 70 angiosarcomas have been identified in the whole country related to vinyl chloride. It is certainly high for that tumor in those areas of exposure.

Mr. OBEY. It is high because there were only 12 known in the world before that.

Dr. RAUSCHER. You are correct.

Mr. OBEY. My point is when you arrive at that figure of 10 percent, in the case of vinyl chloride, are you just considering cancers like angiosarcoma that because of their rarity are directly traceable or are you also considering the fact that there may be other kinds of cancers which, because they were not so rare, and were not readily traceable to occupational causes——

Dr. RAUSCHER. I think it is primarily the former. Clearly, if other kinds of cancer can be associated with that kind of exposure, the 10 percent could increase. But right now the best projection——

Mr. OBEY. What you are saying is that you know at the minimum about 10 percent is related to occupational cancer, but it could very well be higher.

Dr. RAUSCHER. It could be higher. But because of other known factors, such as a big 40 percent chunk with tobacco and alcohol, it does not appear that it would be all that much higher.

Mr. OBEY. Isn't it true that, for instance—I don't smoke, I quit when I got married—but isn't it true that dangerous as cigarettes, for instance, are regarded to be, and I regard them so—isn't it true that when you combine them with something like asbestos you have dynamite on your hands?

Dr. RAUSCHER. Indeed, it is a one plus one equals three phenomenon. It is multiplicative instead of additive.

BUDGETS BY ORGANIZATIONS

Mr. OBEY. Let me ask you some specific questions about your budget. I would like to go through with you the organization of NCI as it presently exists for the record.

When I ask for budget figures and for numbers of positions, I would like to know what you have in these areas this year under the continuing resolution level—without the money that would be allocated from bills we passed earlier in the year.

First, as I understand it, you have the cancer biology program. That was the old pure research program that was in place before the National Cancer Act was passed?

Dr. RAUSCHER. No. This is the Division of Cancer Biology and Diagnosis. It is one of five divisions within the Institute.

Mr. OBEY. What are the goals of that Division, and how many people work in the Division; how much money will they spend in the next year, at the continuing resolution level?

Dr. RAUSCHER. The employment ceiling for that Division is 451 people.

You would like the dollar level also.

Mr. OBEY. Yes.

Dr. RAUSCHER. Let me answer your other question, also.

They have the largest intramural component of any Division in the NCI. A great deal of work is done right on the campus. It is the Division with the smallest budget, as a matter of fact.

In that Division, however, they also have responsibility for a national program in cancer diagnosis. For instance, the three sputum bronchoscope projects I talked about before come from that Division. They are sponsored by that Division.

At the present time the 27 breast cancer detection units around the country are monitored by that Division. Perhaps more importantly than any other program right now is that the breast cancer task force, one of five sponsored by the NCI, is run virtually entirely out of that Division. It is from that study that we have developed this better form of treatment. So that is some of what they do.

Mr. OBEY. Why don't you just prepare for the record an indication of what your general goals are for that.

Dr. RAUSCHER. Fine.

[The information follows:]

GENERAL GOALS—DIVISION OF CANCER BIOLOGY AND DIAGNOSIS

There are four general goals of the Division of Cancer Biology and Diagnosis. In cancer diagnosis we are seeking better methods of screening so that we can find the disease at a stage when our present means of treatment have the best chance of success. Diagnosis research is also working to improve methods, such as X-ray, for the localization of cancer to guide treatment.

In tumor immunology we are trying to understand the interactions between a cancer and the patient's immune system, and to apply this knowledge both in the early detection of the disease and in its treatment.

In breast cancer the goals are better treatment and earlier recognition of the common disease, through clinical research and also through coordinated laboratory study of all aspects of this specific cancer.

The Division supports a research program in the biology of cancer, broadly conceived, including both clinical and basic research, and designed to serve as a standard of excellence for the whole national effort in cancer.

Dr. RAUSCHER. $49.8 million is the operating level for the Division of Cancer Biology and Diagnosis.

Mr. OBEY. How does the Division of Cancer Control relate in size to the other divisions?

Dr. RAUSCHER. Cancer control is a brand new function for the NCI, having been mandated by the acts of 1971 and 1974. Its total budget last year was of the order of $51 million.

Mr. OBEY. How many people?

Dr. RAUSCHER. Forty-nine people onboard now.

Mr. OBEY. You have the Division of Cancer Cause and Prevention. What is their budget and positions?

Dr. RAUSCHER. Cancer Cause and Prevention is the largest Division we have. Their position strength is 507 and their total budget is $125.4 million.

Mr. OBEY. Within that Division of Cancer Cause and Prevention you have three programs; virology, carcinogenesis, and field studies and statistics.

Dr. RAUSCHER. That is right.

Mr. OBEY. Can you tell us what the budget is for each of those programs?

Dr. RAUSCHER. For virology it was approximately $55 million, 220 people; for field studies it was $13 million, 91 people; for carcinogenesis it was about $40 million and 129 people.

Mr. OBEY. Could you supply the committee with a chart showing the information you have given us for those Divisions and the three programs within the Cause and Prevention group?

Dr. RAUSCHER. Yes.

[The information follows:]

RATIONAL CANCER INSTITUTE—ANALYSIS OF FISCAL YEAR 1978 CONGRESSIONAL INCREASES

[In thousands of dollars]

	Operating level as of Jan. 1, 1976				Level based on fiscal year 1978 appropriation			
			Percent of total—				Percent of total—	
	Positions	Amount	Positions	Dollars	Positions	Amount	Positions	Dollars
Division of cancer research and resources and centers	151	$289,917	8.0	42.1	167	$328,259	8.5	43.0
Division of cancer biology and diagnosis	451	49,801	23.9	7.2	461	54,904	23.4	7.2
Division of cancer treatment	463	110,622	24.5	16.1	478	122,067	24.3	16.0
Division of cancer cause and prevention	503	125,450	26.7	18.2	521	138,434	26.5	18.2
Office of the division director	(56)	(9,672)	(3.0)	(1.4)	(58)	(12,672)	(3.0)	(1.7)
Virus cancer	(220)	(661361)	(11.7)	(8.2)	(222)	(58,943)	(11.3)	(7.7)
Carcinogenesis	(126)	(40,060)	(6.7)	(5.8)	(132)	(46,462)	(6.7)	(6.1)
Field studies and statistics	(91)	(13,759)	(4.8)	(4.0)	(99)	(14,759)	(5.0)	(2.0)
Task forces	(10)	(5,598)	(.5)	(.8)	(10)	(5,598)	(.5)	(.7)
Division of cancer control and rehabilitation	49	51,449	2.6	7.5	59	96,806	3.0	7.5
Office of Director, NCI	270	38,034	14.3	5.5	282	39,136	14.3	9.1
NIH management fund		23,041		3.4		23,041		3.0
Total NCI	1,887	638,314	100.0	100.0	1,968	762,647	100.0	100.0

Dr. RAUSCHER. Mr. Obey, I should point out in the Division of Cancer Resources and Centers, much money is also spent for such things as field studies, treatment, and for other categories you mentioned here, and for you to get a larger picture perhaps of the institute's commitments in any of those areas, you may wish that information.

Mr. OBEY. I will supply a specific list of questions so that I get the information as I want it broken down.

Dr. RAUSCHER. Fine.

POSITIONS

Mr. OBEY. Let me start with the question of positions over all at NCI. Last year, you were reported in the New York Times as saying that positions were the greatest problem facing the cancer program. Do you think that is still true?

Dr. RAUSCHER. I do.

INTRAMURAL AND EXTRAMURAL FUNDS

Mr. OBEY. We have all heard in the past how we have to have the right balance between in-house and extramural research. What percentage of the Cancer Institute's work do you think if you had your druthers would ideally be done in-house and how much extramural?

Dr. RAUSCHER. I think the level of in-house effort right now is about right.

Mr. OBEY. Which is what?

Dr. RAUSCHER. I would choose not to expand that much more than it is now. Thirteen percent of our funds, or $100.4 million is used to support in-house activities. That would include management and monitoring of outside programs. I would certainly choose to put more personnel into the in-house management coordination activities of our grants and contracts, of course.

CARCINOGENESIS PROGRAM

Mr. OBEY. Let me ask you about the carcinogenesis program. In 1975 and up until now, they have had how many people?

Dr. RAUSCHER. In the carcinogenesis activities within the Division of Cancer Cause and Prevention, it is 129.

Mr. OBEY. This program is primarily a bioassay program; is that right?

Dr. RAUSCHER. Bioassay, mechanism of action, a good deal of basic research, for that matter.

Mr. OBEY. Isn't it really the major bioassay program in the country? There isn't much of a program going on anyplace else, is there?

Dr. RAUSCHER. It is certainly the major program for the identification and bioassay of chemical carcinogens in the country.

Mr. OBEY. This is a program we rely on to find out what the effect of a chemical is on animals?

Dr. RAUSCHER. That is right; chemicals to which man is exposed.

Mr. OBEY. They are testing about how many chemicals on animals each year?

Dr. RAUSCHER. 520 on test right now.

Mr. OBEY. Is that an annual figure?

Dr. RAUSCHER. No; it is not an annual figure, because it takes 2 to 3 years for one test, so at any one time we have about 500 to 520 on test.

Mr. OBEY. How many do you get results for each year?

Dr. RAUSCHER. At the present time, we have approximately 200 chemicals coming off-line within the next 8 to 12 months, and of that number, about 25 have already gone through pathology and biometric analysis.

Mr. OBEY. This testing is done under contract primarily?

Dr. RAUSCHER. That is right.

Mr. OBEY. With Litton?

Dr. RAUSCHER. No. We have, I believe, 20 different contractors in the country.

Mr. OBEY. Who are they? Why don't you put them in the record?

Dr. RAUSCHER. Certainly.

[The information follows:]

CARCINOGENESIS BIOASSAY CONTRACTORS

Tracor Jitco, Inc., Rockville, Md.
Midwest Research Institute, Kansas City, Mo.
Dow Chemical Co., Midland, Mich.
ITT Research Institute, Chicago, Ill.
Stanford Research Institute, Stanford, Calif.
Mason Research Institute, Worcester, Mass.
Papanicolaou Cancer Research Institute, Miami, Fla.
Battelle Memorial Institute, Richland, Wash.
Litton Bionetics, Inc., Bethesda, Md.
Southern Research Institute, Birmingham, Ala.
Gulf South Research Institute, Baton Rouge, La.
Hazleton Laboratories, Inc., Vienna, Va.
University of Cincinnati, Cincinnati, Ohio
Temple University, Philadelphia, Pa.
Howard University, Washington, D.C.
New York University Medical Center, New York, N.Y.
University of Nebraska, Omaha, Nebr.
University of California at San Diego, San Diego, Calif.
University of Chicago, Chicago, Ill.
U.S. Energy Research and Development Administration, Oak Ridge National Laboratories, Oak Ridge, Tenn.
Industrial Biotest Laboratory, Inc., Northbrook, Ill.

Mr. OBEY. Just tell us now who the major one is.

Dr. RAUSCHER. Tracor Jitco is the prime contractor that helps us manage and monitor the individual contractors that actually do the testing. Each individual contractor has anywhere from eight or nine new compounds to test per year.

CHEMICAL TESTING

Mr. OBEY. You mentioned, I think earlier, and would you explain how you decide which chemicals you are going to run tests on, who you consult before that is determined?

Dr. RAUSCHER. Yes. We have actually a standing compound selection committee. This is going to be expanded, incidentally, in the near future to include people not only from other Government agencies that are already members but from industry as well.

So that is the mechanism that we use to analyze the various input into what the chemicals will be.

Mr. OBEY. What are the chemicals you look at before you actually set your list that is going to be tested?

Dr. RAUSCHER. There are some 200,000 chemicals produced each year, and 5,000 to 10,000 of those are produced in quantities of 1 ton or more. It is certainly representative from that group that we think carry the greatest probability of contamination of the environment.

Mr. OBEY. One ton or more is how many chemicals?

Dr. RAUSCHER. Between five and ten thousand. It is a soft figure, I understand, but it is soft for various reasons.

Mr. OBEY. If you were to look at those you are really most concerned about, what would the number be, the number that you would like to get at right away if you could?

Dr. RAUSCHER. Well, it would certainly be in the hundreds, anyway. When it is known, we take a look at the chemical structure. If the structure is reasonably similar to a known carcinogen, it becomes a prime candidate for testing. We take a look at the amount and type of exposure to people by a chemical. That would influence the priority as well.

RED DYE NO. 2—RED DYE NO. 40

Mr. OBEY. Let me ask you a question about red dye No. 2, which has been banned. I understand that red dye No. 40 is being substituted in many cases.

Dr. RAUSCHER. I understand that is the plan; yes.

Mr. OBEY. One scientist at NCI said No. 40 may be more dangerous than No. 2. Would you agree with that or not?

Dr. RAUSCHER. I have not seen the data. I understand that some of our people have examined red dye No. 40 in what we call our very short-term, or as you well know, the mutagenesis assays.

Mr. OBEY. What tests have you done at NCI on 40?

Dr. RAUSCHER. Some of our people have taken a look at red No. 40 in the short-term test in vitro transformation systems, possibly in mutagenesis assays, but as far as I know, we have not tested red No. 40 in a long term test of 2½ to 3 years.

Mr. OBEY. Haven't we known for almost a decade that No. 2 is in controversy and might be knocked out at any time?

Dr. RAUSCHER. It has been in controversy in various countries in the world.

Mr. OBEY. It has been in controversy as long as I have been in Congress. Why wouldn't NCI be doing more testing on something which people knew was going to be used as a substitute?

Dr. RAUSCHER. Red dye No. 2 has been tested, as you know, by the FDA. That is one reason we didn't test it.

Mr. OBEY. If you know that No. 2 is under controversy, why wouldn't NCI be doing more testing on something like No. 40, knowing that if No. 2 is knocked out, No. 40 might be substituted?

Dr. RAUSCHER. I think the same question can be asked of all the other chemicals that we have on test. It is a matter of selecting those which have the highest probability of having a deleterious impact. Red No. 40, if it is not on test, was not in that ballpark.

Mr. OBEY. But that is my question: why wasn't it? Because it would seem to me that in fact there was great controversy about 2 or 3 years ago, and if in fact there is now some question about the chemical which is going to be used as a substitute, it would seem to me somewhere along the line that gap should have been filled.

Dr. RAUSCHER. I think part of the answer to that is that the data presented on red No. 40 to FDA appeared so good that the FDA did

provide a permanent clearance for it. Many of these chemicals are tested by the sponsor.

ENVIRONMENTAL CARCINOGENESIS

Mr. OBEY. Let me ask you what you meant when you said if we had regulatory authority 17 percent would be grossly inadequate? What did you mean by that?

Dr. RAUSCHER. When you speak of a national program in environmental carcinogenesis, I think you must speak of it in terms of the basic research and testing that goes into that kind of program as well as the use of those research results through regulatory channels. We have no responsibilities or mandate or authority for the regulation aspect of it, as you know.

If we did, then I think our budget would have to be doubled or tripled. What I am saying is that the 17 percent or $124 million approximately for research into mechanisms of environmental chemical carcinogenesis, in view of opportunities in other parts of the program, is about right.

Mr. OBEY. What I am trying to get at is were you suggesting that while you might be spending the proper amount, that other agencies of Government who do have the responsibility for regulation of chemicals perhaps ought to be spending more?

Dr. RAUSCHER. I was not suggesting that Mr. Obey, truthfully.

Mr. OBEY. I just thought you might have been, and that is why I was confused by your statement.

Dr. RAUSCHER. No.

CARCINOGENESIS TESTING

Mr. OBEY. In that carcinogenesis program, how many chemicals have you completed tests on but you don't yet have written reports? In other words, you have given the chemical to an animal for its normal life span; you sacrificed the animal but haven't completed pathology on it. How many?

Dr. RAUSCHER. There are 203 chemicals that are now off test and of that number about 25 have gone through the complete pathology and the biometric analysis. They are in the process of being written up and should come off-line within the next 4 months approximately. The others have still not gone into pathology or are just going into pathology.

Mr. OBEY. Why the lag?

Dr. RAUSCHER. Because in many cases some of them have just come off. In other cases——

Mr. OBEY. How many have come off longer than 6 months?

Dr. RAUSCHER. I am afraid I would be guessing too much to be accurate.

Mr. OBEY. Do you have any idea how many came off more than a year ago?

Dr. RAUSCHER. I don't think any.

Mr. OBEY. I would like you to supply that for the record.
Dr. RAUSCHER. All right.
[The information follows.]

BIOASSAY TESTING

At the present time there are 169 chemicals which have come off test more than 6 months ago. Of these 169 chemicals, 129 have been off test for 12 months or more. This is to say that all testing has been completed with the exception of pathology and biometric analysis.

Mr. OBEY. Would you give us a list for which chemicals are still in that category?
Dr. RAUSCHER. Yes, of course.
Mr. OBEY. And can you tell us who are exposed to them?
Dr. RAUSCHER. Yes, of course. By who are exposed to them?
Mr. OBEY. Where people would run into those chemicals.
Dr. RAUSCHER. Fine; yes.
[The information follows:]

CHEMICALS ON TEST AND EXPOSURE TO THEM: MATERIALS FOR WHICH ALL ANIMALS HAVE EXPIRED BUT FOR WHICH HISTOPATHOLOGY AND BIOMETRIC ANALYSES HAVE NOT YET BEEN COMPLETED

PHARMACEUTICALS AND RELATED SUBSTANCES

Animals expired <6 mo ago	Animals expired >6<12 mo ago	Animals expired >12 mo ago
Nithiazide	EDTA, trisodium salt	Urea
Acronycine	Proflavin Hydrochloride	L-Arginine Glutamate
Phenestrin	2-Amino-5-nitrothiazole	Aspirin-Phenacetin-Caffeine
MAAM	β-nitropropionic acid	Iodoform
Tolazamide	α-Bromo-α-ethylbutyryl carbamide	Emetine
Acetohexamide	Sodium Iodomethane Sufonate	5-Azacytidine
	Lithocholic Acid	Imidazole Mustard
	β-Deoxythioguanasine	ICRF-159
	Tolbutamide	Isophosphamide
	Ethionamide	Streptozotocin
	Chloropropamide	Chlorambucil
	3-Amino-4-ethoxyacetanilide	Methotrexate
		Actinomycin-D
		Daunomycin
		Mitomycin
		4-(Dimethyltriazene)imidazole-5-carboxamide
		Arabinosylcytosine
		1-Acetyl-2-picolinoyl Hydrazine
		1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea
		Dibromomannitol
		1,3-bis(chloroethyl)nitrosourea
		6-Methylmercaptopurine Riboside
		Dibromodulcitol
		Carbanilide-4,4′-diacetyl bis(amidino hydrazone)dimethane sulfonate
		Guanazole
		Uracil Mustard
		Hydroxyurea
		Vinblastine
		Melphalan
		Vincristine
		Dichloromethanotrexate
		6-Mercaptopurine
		Prednisone
		Cyclophosphamide
		Cytoxal Alcohol
		o-Melphalan
		Estradiol Mustard
		Procarbazine (Natulan)
		Azathioprine
		1-phenyl-2-thiourea
		Pyrazinamide
		L-Tryptophan
		Myleran
		Pyridium
		Daraprim
		Phenformin

CHEMICALS ON TEST AND EXPOSURE TO THEM: MATERIALS FOR WHICH ALL ANIMALS HAVE EXPIRED BUT FOR WHICH HISTOPATHOLOGY AND BIOMETRIC ANALYSES HAVE NOT YET BEEN COMPLETED—Continued

Animals expired <6 mo ago	Animals expired >6<12 mo ago	Animals expired >12 mo ago
FOOD ADDITIVES		
		Dulcin Sodium Nitrite
SOLVENTS		
		Carbon Tetrachloride Hexachloroethane Carbon Disulfide Trichlorofluoromethane Sulfolene Acetamide Methylchloroform 1,2-Dichloroethane 1,1,2-Trichloroethane Tetrachloroethylene 1,1-Dichloroethane 1,1,2,2-Tetrachloroethane
PESTICIDES AND RELATED SUBSTANCES		
p-Dioxane Piperonyl sulfoxide Methyl parathion CCC Phthalic anhydride Ledate Phthalamide Dibenzo-p-Dioxin Dichlorodibenzodioxin (DCDD)	Triphenyl Tin Hydroxide 2,2-Dimethylhydrazide Succinic Acid 2,4,6-Trichlorophenol Ethylan Azobenzene Piperonyl butoxide	Chloropicrin Picloram Phosphamidon Nitrofen Aldrin Gusathion Captan Dieldrin Endrin Gardona Kepone (Chlordecone) Parathion Photodieldrin Malathion Lindane Toxaphene Daconil Amiben Dibromochloropropane (DBCP) PCNB Methoxychlor Endosulfan (thiodane) Chlorobenzilate DDT DDD DDE Kelthane Dioxathion Bayluscide Vegadex 1,1,2,2-tetrachloroethane Trifluralin Zectran
POSITIVE CONTROL SUBSTANCES		
	2 AAF Amitrole	Amitrole 2 AAF Safrole
DYES AND DYE INTERMEDIATES		
2,4-Dimethoxyanilin 4,4'-chloroacetyl-(acetanilide) 1-phenyl-3-methyl-5-pyrazolone Amunthrene 2,4-Toluene diamine 2,4,5-Trimethylaniline	p-Cresidine Aniline Hydrochloride 3-Amino-9-ethylcarbazole Diaryl Anilide Yellow	4,4'-bis(diethylamino)benzopheno 2-nitro-p-phenylene diamine p-Chloroaniline 1-Nitroanaphthalene m-Cresidine N,N'-Dimethyl-p-nitrosroniline 5-Nitro-o-toluidine 2,4-Dinitrotoluene 2-Aminoanthraquinone 1-Amino-2-methylanthraquinone p-Aminodiphenyl Amine

CHEMICALS ON TEST AND EXPOSURE TO THEM: MATERIALS FOR WHICH ALL ANIMALS HAVE EXPIRED BUT FOR WHICH HISTOPATHOLOGY AND BIOMETRIC ANALYSES HAVE NOT YET BEEN COMPLETED—Continued

INDUSTRIAL COMPOUNDS AND INTERMEDIATES

Animals expired <6 mo ago	Animals expired >6<12 mo ago	Animals expired >12 mo ago
Trimethyl Phosphate	β-Nitrostyrene	3-Chloroprene
Styrene	4-Chloro-m-phenylene Diamine	1,1,3-Trimethyl-2-thiourea
N,N'-Diethyl Thiourea	2-Chloro-p-phenylene Diamine Sulfate	p-Nitroso Diphenylamine
Pivalolactone	3,3'-Dimethoxybenzidine Diisocyanate	NTA
Ethylene Tellurac	p-Quinone Dioxime	NTA, Trisodium salt
		Adipamide
		Hexanamide
		p-Tolylurea

MISCELLANEOUS SUBSTANCES HAVING USE IN ORGANIC SYNTHESIS

3-(chloromethyl)pyridine Hydrochloride	1,2,3-Benzotriazole	4,4'-Thiodianiline
4-Nitro-o-phenylene Diamine	n-(1-naphthyl)ethylenediamine dihydrochloride	4,4'-Sulfonyldianiline
	1,5-Naphthalene Diamine	4,4'-Methylenebis (N,N'-dimethylaniline)
	Hydrazobenzene	Dibutyl Tin Diacetate
	6-Nitrobenzimidazole	3-Chloro-p-toluidine
	2-Methyl-1-nitroanthraquinone	5-Chloro-o-toluidine
	2,4-Diaminoanisole Sulfate	5-Nitro-o-anisidine
	N,N'-Dicyclohexylthourea	5-Nitroacenaphthene
	4-Nitroanthranilic Acid	2,5-Dithiourea
	Cupferron	4-Chloro-o-phenylene Diamine
	p-(dimethylamino)-benzidine diazosodium sulfonate	n-Butylurea
		Dulcin/L-Arginine Glutamate
		n-Butylurea/Sodium Nitrite
		3-Nitro-p-acetophentide

Materials for which reports are being prepared at this time (all "greater than" 12 months since all animals have expired).

Pharmaceuticals

2-methyl-aziridine.
Sodium azide.

Food additives

Saccharin.
Sodium cyclamate.

Solvents

Ethylene carbonate.
Vinylene carbonate.
Trichloroethylene.
Chloroform.

Pesticides and Related Substances

Chlordane.
Heptachlor.
Dichlorvos (Vapona).
Dimethoate.
Bis (2-hydroxyethyl) dithicoarbamine acid, potassium salt.
Avadex.
Bis(2-chloroethyl)ether.
Mirex.
4-chloro-4'-aminodiphenyl ether.

Dyes and Dye Intermediates

Glycerol monochlorohydrin.
Benzoguanamine.
o-Toluidine HCl.
1-chloro-2-nitrobenzene.
1-chloro-2,4-dinitrobenzene.
1-chloro-4-nitrobenzene.
2,4,6-trichloroaniline.
2,4-Xylidine HCl.
2,5-Xylidine HCl.

m-Phenylene diamine 2HCl.
4-chloro-o-toluidine HCl.
2,4,5-Trimethylaniline HCl.
2,4,6-Trimethylaniline HCl.
m-Toluidine HCl.
o-Phenylene diamine 2HCl.

Industrial Compounds and Intermediates

Propane Sultone.
Ethylene Thiourea.
Semicarbazide HCl.
Propylene imine.
Dithiooxamide.
Thiosemicarbazide.
Dicyclopentadiene dioxide.
2,5-Dimethoxy-4' aminostilbene.
Tetrofluro-m-phenylene diamine 2HCl.
3,3',4,4'-Tetraaminodiphenyl 4HCl.
p-Toludine Hydrochloride.
2,4,-Diaminotoluene.
4,4'-Methylene-bis-(2-chloraniline) HCl.

Positive Control Substances

The materials classed as "pharmaceuticals and related substances" or "food additives" are materials to which individual members of the general population might have intermittent or occasional exposures. Those materials classed as "solvents," "industrial compounds and intermediates" or "miscellaneous substances having use in organic synthesis" represent primarily occupational exposures where small segments of society may encounter the substances with considerable frequency. Many of the latter group of substances may also come into occasional contact with the general population (for example, certain chlorinated hydrocarbons having massive usage as industrial solvents but to which the general population is occasionally exposed as a result of dry cleaning operations).

Pesticides in general have both occupational and general population exposures. The relative proportions involved are heavily dependent on the specific compound chosen. The "dyes and dye stuff intermediates" represent primarily industrial exposures, although we know very little about the exposure of the general population to specific dyes or their breakdown products.

The positive control compounds listed are materials to which no significant human exposure would be anticipated except for those individuals engaged in cancer research activities.

RESOURCES NEEDS—CARCINOGENESIS

Mr. OBEY. Does that carcinogenesis program make requests to you each year on how much money and positions they feel they need in order to do the job properly?

Dr. RAUSCHER. Yes.

Mr. OBEY. What was that request for fiscal 1977?

Dr. RAUSCHER. Let me make some comments here while we are trying to be as accurate as we can.

Mr. OBEY. What I am getting at is I understand that Dr. Saffiotti feels that he needs a minimum of about 80 more people in order to get that program functioning as it should. Is that right?

Dr. RAUSCHER. I think Dr. Saffiotti could easily use many more people. Eighty sounds very, very high to me. My problem, of course, in every year I have been associated with this program, is we rarely get 80 for the entire institute. This year, as a matter of fact, it will be 81 if we get all that we have been allowed by the Congress.

Dr. Saffiotti has consistently received a very high priority. He tells me he really can't take any more money if he doesn't get the manpower, and I agree with him.

Mr. OBEY. I am not talking about money; I am talking about personnel.

Dr. RAUSCHER. We asked for 160 people against the 129 that we will get. Dr. Saffiotti told me several weeks ago, after I had asked him for this, that in the best world's budget he could use effectively another $15 million provided again that the people went with it. No more than that.

Mr. OBEY. Forget the bucks; I am talking about people. How many people? Why don't you supply that for the record?

[The information follows]

PERSONNEL REQUIREMENT FOR CARCINOGENESIS PROGRAM

Dr. Saffiotti, associate director for carcinogenesis, has requested an additional 65 positions for the most effective operation of the carcinogenesis program. While I concur that this program does require new positions, I feel that we must maintain the proper balance among the research programs of the national cancer program. Within finite resources, I have tried to maintain this balance based upon the advice of advisory groups and NCI staff. The carcinogenesis program will continue to receive high priority, but in order to maintain the program balance within the total national cancer program, I believe that an additional 35 positions for Dr. Saffiotti's program can be very effectively utilized.

TRICHLOROETHYLENE

Mr. OBEY. Did you mention trichloroethylene earlier today?

Dr. RAUSCHER. Yes; I did.

Mr. OBEY. When Dr. Korn was here, I asked him about trichloroethylene, and they just issued a proposed standard for that chemical which a lot of people think is too high to protect people if it is in fact carcinogentic. He indicated that the information which he got from NCI really wasn't all that useful for a variety of reasons. What can we do to make that kind of information more useful to people who are doing the regulating?

Dr. RAUSCHER. The problem with trichloroethylene is the problem we have with every weak carcinogen. I can look at the data and analyze it, and there is a suggestion, as there seemed to be with cyclamates, that there are more tumors in the treated group than in the control group, but it is not as black and white as we would like it. I don't know what can be done.

There is virtually nothing you can do to increase the sensitivity of the tests we are using now so that the data will come out more black and white if, in fact, you are dealing with one of those borderline chemicals. With tobacco it is easy; with other chemicals it is very easy, but not with that one.

EPIDEMIOLOGY PERSONNEL

Mr. OBEY. You have talked about the necessity to upgrade the epidemiology and etiology programs so we can really find out what is true with mice is true with human beings. I understand Dr. Fraumeni will be heading a new effort in that area. How many professionals work for him?

Dr. RAUSCHER. We have just created that branch within the past several months, and he will have on the order of 15 people who will form the nucleus of that branch.

Mr. OBEY. How many professionals?

Dr. RAUSCHER. He must have about 10.

Mr. OBEY. My information was four.

Dr. RAUSCHER. I will provide it for the record.

[The information follows:]

PROFESSIONAL PERSONNEL FOR ENVIRONMENTAL EPIDEMIOLOGY BRANCH

Dr. Fraumeni currently has six professionals on his staff: two physician-epidemiologists, two statisticians, one veterinarian and one computer analyst. Four of these professionals are working on the environmental problem. Dr. Fraumeni has requested 17 additional full-time people, including 5 epidemiologists and/or statisticians and 3 computer programmers. The other nine positions would be support personnel.

Mr. OBEY. My question is why is it so small? I had been told, for instance, when the question of fluoridation of water was raised a few months ago, that a lot of the work in that section virtually stopped while they had to respond to this question. To me that would indicate that you don't have enough people.

Dr. RAUSCHER. We certainly do not have enough people, especially in the area of epidemiology.

Mr. OBEY. Has Dr. Fraumeni given you an indication of how many people and how much more money he needs to get the program going?

Dr. RAUSCHER. No; I have asked him exactly for that, and he will give it to me within the next several weeks.

Mr. OBEY. Any quesstimate as to how many people he is going to be asking for?

Dr. RAUSCHER. Knowing Joe, I think it will be on the order of 15 or 20.

Mr. OBEY. Couldn't you take care of that small number of people under your 1976 appropriation?

Dr. RAUSCHER. I don't think there is any way I could do that under the 1976 appropriation. First of all, you need trained epidemiologists. There are few of those in the country, as a matter of fact. It simply does not do to say that one program of the Institute is less important than this one and move people over. Those people are not trained to do it and oftentimes don't want to do it, and if you force them to do it, they don't do it well. I see no way I can do that within the 1976 budget.

ENVIRONMENTAL CANCER ADVISERS

Mr. OBEY. Who are the chief advisers on environmental cancer?

Dr. RAUSCHER. We have a subcommittee to the National Cancer Advisory Board, and there are some 23 of the Nation's key people in environmental carcinogenesis. This is headed by Dr. Phillippe Shubik, a member of the Advisory Board as well. I can give you a list of the names for the record if you like.

[The information follows:]

ENVIRONMENTAL CARCINOGENESIS SUBCOMMITTEE, SUBCOMMITTEE OF THE NATIONAL CANCER ADVISORY BOARD

Chairman

Dr. Philippe Shubik
Director, The Eppley Institute For Research in Cancer
University of Nebraska
Omaha, Nebraska 68105

Executive Secretary

Dr. W. Gary Flamm
Assistant Director, Division of Cancer Cause and Prevention
National Cancer Institute
Bethesda, Maryland 20014

Committee Members

Dr. William O. Baker
President, Bell Telephone Laboratories, Inc.
600 Mountain Avenue
Murray Hill, New Jersey 07974

Dr. Edward J. Burger, Jr.
Senior Policy Analyst
Science & Technology Policy Office
The National Science Foundation
1800 G Street, N.W.
Washington, D.C. 20550

Dr. Irving M. London
Director, Harvard-MIT Program in Health Sciences & Technology
Building 16–512
77 Massachusetts Avenue
Cambridge, Massachusetts 02139

Dr. William E. Powers
Director, Division of Radiation Oncology
Mallinckrodt Institute of Radiology
Washington University School of Medicine
St. Louis, Missouri 63110

Consultants

Dr. Roy Albert
Deputy Assistant Administrator
Environmental Protection Agency
Washington, D.C. 20460

Dr. Herbert Blumenthal
Division of Toxicology
Food and Drug Administration
Federal Building 8—Room 5022
200 C Street, S.W.
Washington, D.C. 20204

Dr. Arnold L. Brown
Chairman, Department of Experimental Pathology
Mayo Clinic
Rochester, Minnesota 55901

Dr. David B. Clayson
The Eppley Institute for Research in Cancer
University of Nebraska
Omaha, Nebraska 68105

Prof. Jerome Cornfield
Biostatistics Center
7979 Old Georgetown Road
Bethesda, Maryland 20014

Dr. Hans L. Falk
NIEHS
P.O. Box 12233
Research Triangle Park, N.C. 27709

Dr. Takeshi Hirayama
Chief, Epidemiology Division
National Cancer Center Research Institute
Tsukiji 5-chome
Chuo-ku, Tokyo 104, Japan

Dr. Peter N. Magee
Fels Research Institute
Temple University School of Medicine
Philadelphia, Pennsylvania 19140

Mr. Arthur McGee
Stanford Research Institute
333 Ravenswood Avenue
Menlo Park, California 94025

Dr. Norton Nelson
Director, Institute of Environmental Medicine
New York—University Medical Center
550 First Avenue
New York, New York 10016

Dr. Henry C. Pitot, III
McArdle Laboratory
School of Medicine
University of Wisconsin
Madison, Wisconsin 53706

Dr. David Rall
Director, NIEHS
P.O. Box 12233
Research Triangle Park, N.C. 27709

Dr. Irving J. Selikoff
Director, Division of Environmental Medicine
Department of Community Medicine
Mt. Sinai School of Medicine of the City University of New York
5th Avenue and 100th Street
New York, New York 10029

Dr. Michael B. Shimkin
Professor of Community Medicine and Oncology
School of Medicine
University of California, San Diego
La Jolla, California 92093

Dr. Bernard Weinstein
Professor, Department of Medicine
College of Physicians & Surgeons
Columbia University
New York, New York 10032

Dr. Gerald N. Wogan
Professor of Food Toxicology
Massachusetts Institute of Technology
77 Massachusetts Avenue
Cambridge, Massachusetts 02139

Dr. Ernst Wynder
American Health Foundation
1370 Avenue of the Americas
New York, New York 10019

Mr. OBEY. Who is Dr. Shubik, and what is his position?

Dr. RAUSCHER. He is director of the Eppley Institute for Cancer Research in Omaha, Nebr.

Mr. OBEY. What is his position in NCI?

Dr. RAUSCHER. He is a member of the National Cancer Advisory Board appointed by the President.

Mr. OBEY. As a member or chairman?

Dr. RAUSCHER. He is a member. He is chairman of the board subcommittee on environmental carcinogenesis. That is the group, by the way, Mr. Obey, that I have convened to try to better define carcinogenesis.

Mr. OBEY. Does he do consultation for industries which use chemicals which might be suspected of being a problem?

Dr. RAUSCHER. He has consulted to private industry in the past; yes.

Mr. OBEY. Would you list the industries that he has consulted for?

Dr. RAUSCHER. I believe I can provide that for the record; yes.

Dr. OBEY. I think we should know.

Were you going to say something?

Mr. BROWNING. We wouldn't know that, but maybe we could get that information.

Dr. RAUSCHER. That is why I hesitated.

Mr. OBEY. You don't know that?

Mr. BROWNING. I am sure we don't.

Mr. OBEY. Shouldn't you know that?

Dr. RAUSCHER. We have the industries he has consulted for listed in his conflict-of-interest statement, as we have for any member of the board on one of our committees.

Mr. OBEY. What did you mean, then, by you didn't know.

Mr. BROWNING. I am sorry; I wasn't sure. I withdraw that.

[The information follows:]

INDUSTRIES CONSULTED FOR BY DR. PHILIPPE A. SHUBIK

Organization	*Title or kind of position*
Royal Crown Cola	Consultant.
Abbott Laboratories	Do.
Miles Laboratories	Do.
General Foods	Scientific Advisory Board.
Procter & Gamble	Consultant
Colgate-Palmolive Co	Do.
Extract Manufacturers Association	Do.
Calorie Control Council	Do.

Mr. OBEY. Could you tell us what consulting or contracting for private industry is being done by members of the National Cancer Advisory Board other than Dr. Shubik?

Dr. RAUSCHER. Each year the members of the National Cancer Advisory Board submit to the NCI a confidential statement of employment and financial interests. Based on this information the following members are providing consulting or contracting activities for private industry.

Name, organization, title or kind of position:
Frank J. Dixon, Eli Lilly & Co., consultant.
Jonathan E. Rhoades, Pennwall Corp., director.

Mr. OBEY. Do you also provide grants and contract work for his institute in Nebraska?

Dr. RAUSCHER. Yes, we do.

Mr. OBEY. How much?

Dr. RAUSCHER. It is of the order of about $3 million for the carcinogenesis testing and mechanisms of action studies that he does.

Mr. OBEY. Any other funds?

Dr. RAUSCHER. I would think so, but I am not sure.

Mr. OBEY. Why don't you supply for the record how much that is?

[The information follows:]

FUNDS PROVIDED TO EPPLEY INSTITUTE FOR CANCER RESEARCH

In fiscal year 1975, the University of Nebraska, including the medical center located at Omaha, Nebr., received funds for 11 research grants totaling $447,000, 1 training grant for $92,000, and 2 research and development contracts totaling $3,011,453.

Mr. OBEY. In evaluating that institute before you awarded the contract, did you determine if he ever did bioassay work on ethylenedibromide?

Dr. RAUSCHER. I don't think so, but I will check with the program leaders.

[The information follows:]

RESEARCH ON ETHYLENEDIBROMIDE

It is normal procedure to determine what bioassay work has been accomplished before any chemical is placed into the NCI bioassay system. This is accomplished primarily through a literature search of scientific data. Since the Eppley Institute contract was not considered for research on ethylenedibromide, the review of previous bioassay work of this chemical was not a consideration to the award, and therefore, a determination of whether that institute did any work on ethylenedibromide before awarding the contract was not made.

Mr. OBEY. Could you tell us for the record what the Division of Cancer Treatment does?

CANCER TREATMENT DIVISION

Dr. RAUSCHER. The primary objectives of the Division of Cancer Treatment (DCT) are the development of new treatments for cancer including drugs, but also other modalities such as newer forms of radiotherapy and immunotherapy. The Division aims to maximize use of existing treatments by clinical research examining their use in combination with each other at an early stage of cancer development. These goals are pursued through ongoing intramural programs of the DTC and through contracts and grants with universities, industry, and other institutions.

The Division conducts an extensive search for new anticancer agents. As a part of this activity, studies of cell behavior are integrated with those concerning the effects of chemotherapeutic agents. Improved methods for screening of new agents are developed. Possible models for appropriate screens to evaluate the safety and efficacy of drug combinations and combined modality therapy are explored.

Better clinical results are achieved when combinations of chemotherapeutic agents are used, and when drugs are used in conjunction with surgery, radiation therapy, and immunotherapy. Early use of combined modality therapy is now strongly emphasized and is expected to lead to more successful clinical control, particularly of the slower growing, more drug-resistant tumors. Development of modalities used in combination with chemotherapy is also a responsibility of DTC.

New scientific findings lead to modifications of established research programs and may present new opportunities for clinical explorations. Cancer therapy activities elsewhere in the Nation and around the world are therefore constantly monitored and related to DCT concerns and programs.

Mr. OBEY. Then you have the Division of Cancer Resources and Centers. How many people and how many positions?

Dr. RAUSCHER. The Division of Cancer Research Resources and Centers has a ceiling of 151 positions for fiscal year 1976. As of February 29, there were 149 permanent full-time people on board.

Mr. OBEY. Could you tell us for the record what this Division does?

Dr. RAUSCHER. The Division of Cancer Research Resources and Centers administers research programs that encompass the full scope of laboratory and clinical cancer research, manpower programs to develop research and clinical personnel needed to carry out the mandate of the National Cancer Act, and a centers program to develop organizational resources and facilities for enhancing the Nation's cancer research and cancer control efforts. Within its guidelines, the Division of Cancer Research Resources and Centers emphasizes support of the most meritorious research, resource, and manpower initiatives conceived and promulgated by investigators outside the Federal establishment. These initiatives include research in cancer epidemiology, chemical and viral carcinogenesis, tumor biology, radiation biology, immunology, diagnosis, drug development, and cancer therapy. The Division supports targeted programs of research on bladder, large bowel, prostatic, and pancreatic cancer. The Division fulfills its manpower development responsibilities by making Research Career and Research Career Development Awards and by awarding grants in the Clinical Cancer Education program and by providing National Research Service Awards for individual fellowships and for institutional programs. The Division addressed its

responsibility in resource development by making grants for core support in specialized and comprehensive cancer centers, by exploratory grants, and by providing grants for the construction of facilities for laboratory and clinical cancer research.

CLINICAL RESEARCH CENTERS

Mr. OBEY. The National Cancer Act of 1971 authorized the NCI Director to establish 15 new centers for clinical research, training, and demonstration of advanced diagnostic and treatment methods relating to cancer. An amendment to the act in 1974 removed the restriction on the number of new centers.

Both the Senate Panel of Consultants on the Conquest of Cancer and the National Cancer Advisory Board wanted cancer centers to achieve an appropriate geographic distribution. Has NCI defined "appropriate geographic distribution?" What factors will influence the distribution of comprehensive cancer centers?

Dr. RAUSCHER. The National Cancer Institute has not yet been able to determine all the factors necessary to define the "appropriate geographic distribution" for comprehensive cancer centers. Demographic characteristics, such as population density and geographic barriers, must be considered as well as such factors as cancer incidence, mortality rates, existing patient referral patterns, ethnic, and other populations, and socioeconomic factors affecting education and information dissemination. Also to be considered are such important factors as special research needs or capabilities of a region and the current or potential availability of scientific and medical expertise. Since comprehensive cancer centers are expected to coordinate the upgrading of cancer care through programs of cancer education, training, demonstration of the best possible cancer detection, diagnosis, and treatment, and dissemination of cancer information, the availability of excellence in the scientific environment of the cancer center is extremely important.

Mr. OBEY. When commenting on how adequately the comprehensive centers are geographically distributed, NCI refers to the number of people located near a center. Last year NCI reported that about 31 comprehensive centers would be needed to serve about 180 million people. What services do the comprehensive centers provide to the population in their areas? What population is served by the 17 existing centers? Where will the 31 centers have to be located to serve 180 million people?

Dr. RAUSCHER. Comprehensive cancer centers are expected to develop the capability to furnish multidisciplinary programs for research as well as for the demonstration of the latest techniques of cancer diagnosis and treatment and programs in continuing medical education for professionals and allied health personnel, dissemination of cancer information to the public, professional consultation, and specialized cancer diagnostic and treatment services required by referring physicians in the community to manage complex or unusual cancer problems. Centers provide cancer data gathering capabilities and cooperate with affiliated agencies to carry out mutually developed cancer projects tailored to fit the particular needs and resources of

that geographical area. The extent and kinds of services presently provided by the 17 comprehensive cancer centers to their surrounding areas vary greatly depending on the differing needs which exist in each area, the differing resources available, and the differing stages of development of the various comprehensive cancer center programs.

It is estimated that 106.5 million persons live within a 120-mile radius of a center. This estimate is currently being used by NCI as the approximate potential population serviced by these centers until better information can be developed.

NCI has conducted a number of analyses, using different sets of criteria for selection of geographic location of future comprehensive centers. Among the factors are care delivery patterns, existing centers of excellence, aggregations of population, numbers of primary care physicians, and interest on the part of eligible institutions. The final set of criteria, their application and timing of implementation involves complex and far-reaching policy issues.

Our report last year on the potential number of centers needed to serve 180 million people was based on a preliminary analysis of data on aggregation of population, the current locations of comprehensive centers, and an estimate of existing institutions with potential for development. Different iterations of this analysis put the potential ceners in different locations, but the overall conclusion then was that it was possible to come within 120 miles of 180 million people with about 30–35 centers, including the 17 now designated.

Until we have finalized the policies referred to above, we are unable to cite the required number as well as specific locations of future centers.

Mr. OBEY. The actual designation of a research institution as a comprehensive center is done by the NCI Director after a review by the National Center Advisory Board. The Board has determined that NCI's comprehensive centers should meet specific criteria, ranging from a distinct administration to an excellent research environment. Do prospective centers go through the usual NIH peer review? How strictly are prospective centers judged against the Board's criteria? How often are centers reviewed after their designation?

Dr. RAUSCHER. All cancer centers, prospective or already recognized, must compete for funding through the usual NIH peer review system although this review does not include consideration as to whether or not they should be designated as comprehensive cancer centers. Prospective comprehensive cancer centers are carefully and thoroughly reviewed by the National Cancer Advisory Board as well as by NCI staff to determine how completely they meet the 10 criteria of the Board which are requisite for recognition as a comprehensive cancer center. Each center is reviewed every 3 to 5 years following its designation as a comprehensive cancer center.

Mr. OBEY. Comprehensive centers receive grants to support their central or core functions. These grants, like most other NIH grants, are awarded after application by the institution and the traditional

peer review for scientific merit. NCI sponsors only two programs exclusively for comprehensive centers—a contract-supported communications network and a cancer-control development grant program. Does the designation as a comprehensive center affect an institution's ability to compete for NCI grants or contracts? Has NCI made any long-term funding commitments to the comprehensive centers?

Dr. RAUSCHER. Designation as a comprehensive cancer center does not, in itself, affect the ability of an institution to compete for NCI grants and contracts. However, comprehensive cancer centers, being centers of excellence, generally compete very favorably through the normal NIH peer-review system. NCI has not made any long-term commitments to comprehensive cancer centers.

Mr. OBEY. Comprehensive cancer centers are supposed to demonstrate the latest research findings so that people in their area can have the best in cancer prevention, detection, diagnosis, treatment, and rehabilitation. The centers are also expected to have strong interactions with the medical profession and the general public. Have the comprehensive centers become leaders in their communities for referrals, consultations, education, training, and so forth? What impact has the comprehensive centers program made on getting research findings translated in general medical practice?

Dr. RAUSCHER. Comprehensive cancer center programs vary considerably from place to place, depending on their stage of development. Some centers are long established and others are fairly recently developed. Therefore, the extent to which the comprehensive cancer centers have already become leaders in their communities for referral, consultation, education, training, and so forth, varies from center to center.

NCI is currently developing plans to further assess the impact comprehensive cancer center programs have made on getting research findings translated into general medical practice. Centers are taking a leadership role in helping to develop improved patterns of cancer control throughout their areas of influence. Some centers are very young and are still defining their proper leadership role while others such as M. D. Anderson and Memorial Sloan-Kettering have been demonstrating strong and valued leadership for years. Most have a consultation service or system which is readily available to all general practitioners and specialists. Some centers are bringing in family practitioners to their centers for training. Centers are sending out teaching teams to distant community hospitals and community cancer centers to assist them in improving and updating their cancer treatment procedures.

Many of the centers are interacting with communities and community hospitals to cooperatively develop nurse-oncology training programs. Most centers are taking on the coordinating responsibility to insure that proper radiation therapy standards are being established and maintained. In the area of public information and education, the centers are closely coordinating leadership responsibilities with the American Cancer Society and other community organizations to insure the maximum access of the public to cancer information and edu-

cation. At the present time, each center, in cooperation with the American Cancer Society, is developing an extensive public information service utilizing toll-free telephone lines which will provide both the public and health service professionals with immediate access to accurate cancer information and available patient care resources.

In these and many other ways, the centers very definitely are getting research findings translated into good medical practice.

Mr. OBEY. In some locations such as Chicago, Denver, Washington, and Philadelphia, NCI has designated more than one institution as one comprehensive center. NCI expected these centers to develop a single administrative structure and to serve as a single comprehensive center. How do these centers operate? Have they, in fact, developed into single centers?

Dr. RAUSCHER. NCI has not expected cancer centers composed of more than one major institution to develop a single administrative structure or the operation of all aspects of the center. However, NCI does expect such centers to collaborate in developing operating mechanisms to accomplish certain functions such as community outreach. Each center of this type has approached this organizational problem in different ways to accomplish these specific functions, and the centers are in differing stages of development at the present time.

Mr. OBEY. Certain chemicals, such as food additives, drugs, and pesticides, are required to be proved safe by their manufacturers before they can be approved for marketing. Does NCI have access to the safety data maintained by FDA and EPA for these chemicals?

PROPRIETARY RESTRICTIONS

Dr. RAUSCHER. In most instances, particularly with food additives and drugs, NCI has full access to safety data as maintained by FDA. However, availability of safety data on certain chemicals is precluded by trade secret exemptions of the Freedom of Information Act, and these data may not in all cases be available to NCI. For instance, safety data contained in pesticide petitions to EPA are considered proprietary and subject to trade secret exemption.

Mr. OBEY. If not, shouldn't NCI have access to this information?

Dr. RAUSCHER. Theoretically and logically, yes. In actual practice, however, we believe our liaison with the other agencies helps to insure that information concerning hazard or suspicion of carcinogenicity will come to NCI attention. Accordingly, and as pointed out elsewhere, NCI regards interagency cooperation and liaison to be of critical and fundamental importance.

Mr. OBEY. What impact does this information have on NCI's tests?

Dr. RAUSCHER. NCI now has a mechanism in its chemical selection process which provides other Federal agencies with the opportunity to nominate chemicals for biosssay. In some, perhaps many, instances the basis of the nomination is toxicity data which make the chemical in question suspect. Depending upon the nature of the available information such information might well be used in helping to establish dosage levels at which the chemical should be tested, in deciding the most appropriate route of administration, and in the overall assessment of toxicity and hazard.

CANCER EPIDEMIOLOGY BRANCH

Mr. OBEY. Could you supply for the record, Dr. Fraumeni's plan of where we should be a year from now in the epidemiology branch, how many people, how much money, and what they should be accomplishing?

Dr. RAUSCHER. In the next year Dr. Fraumeni hopes to enlarge and greatly strengthen the epidemiology program at the National Cancer Institute, particularly in environmental studies. The recent demonstration of "clusters" of cancer mortality in certain U.S. communities represents a promising point of departure for studies to formulate and test hypotheses concerning environmental carcinogens. Despite severe shortage of professional staff, the branch is now taking steps to: (1) Enlarge the program of collaborative studies with other agencies—for example, CDC, VA, EPA, NAS, FDA, NIOSH, NCHS—that possess important epidemiologic resources that require active involvement and coordination by NCI; (2) fully utilize national data resources, such as U.S. cancer mortality and morbidity statistics, for descriptive, correlational and analytical studies; (3) undertake more systematically and energetically directly and in collaboration with other groups, appropriate field studies to identify etiologic factors responsible for the high-risk communities identified in the Atlas of cancer mortality for U.S. counties: 1950–69; (4) insure that urgent epidemiologic questions are resolved by the most rapid and efficient means possible, including in-house research, contracts, grants, interagency cooperation, collaboration with the surveillance, epidemiology and end results reporting program units, and other groups around the country; and (5) further develop a comprehensive well-balanced intramural program in cancer epidemiology, with the capacity to conduct and coordinate analytical studies to help settle key questions in cancer etiology; for example, drug and occupational hazards, general environmental exposures (air, water, food), hormonal and immunologic influences, infectious agents, and genetic-familial determinants. Dr. Fraumeni feels the Environmental Epidemiology Branch will require 35 people (this is an increase of 17 over fiscal year 1976) and a total of $5 million (in-house and contracts).

ENVIRONMENTAL CARCINOGENESIS

Mr. OBEY. One problem in identifying which chemicals pose human cancer threats seems to be the lack of generally-accepted principles concerning environmental carcinogenesis. What is NCI doing to develop these principles? What role is the National Cancer Advisory Board's Subcommittee on Environmental Carcinogenesis playing?

Dr. RAUSCHER. The Director of the NCI requested in a letter dated September 19, 1975, to the National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis that the subcommittee under take to provide a functional definition for a chemical carcinogen. The subcommittee has held four meetings on this subject using a wide range of expert consultants representing all disciplines germane to carcinogenesis, and has developed a document, which is in draft form, entitled "General Criteria for Assessing the Evidence for Carcinogenicity of Chemical Substances." A final meeting of the subcommittee will be held to address yet unresolved issues and to finalize their document which will be submited to the Director of the NCI through the NCAB.

Mr. OBEY. Does NCI comment on cancer principles advanced by other Federal agencies, such as EPA and OSHA?

Dr. RAUSCHER. The NCI participates at many levels in the promulgation of cancer principles by regulatory agencies. Interaction between NCI and EPA and OSHA occurs on a scientist-to-scientist basis as well as at top administrative levels. EPA is presently developing internal policy and procedures on chemical carcinogens, and has established the Cancer Assessment Group, on which NCI has membership and will participate. Likewise, representatives from EPA and OSHA participate in NCI efforts to develop generally accepted principles for environmental carcinogenesis.

FREEDOM OF INFORMATION

Mr. OBEY. The principal results of NCI's testing program are scientific reports on the cancerous effects of chemicals on animals. Recently, NCI has started issuing "memoranda of alert" for chemicals identified as carcinogenic in animal tests, followed by detailed, technical reports after all tests are completed. How does the Freedom of Information Act affect NCI's test results, especially interim results? What do these reports cost and how long after testing is completed are they used? Has the NCI received any feedback on the value of the reports?

Dr. RAUSCHER. The Freedom of Information (FOI) Act has no direct effect on NCI's bioassay test results. It does have a considerable effect, however, on the ways in which we release those results to interested parties. Information is released at a much earlier stage under FOI requests than has customarily been done in the past. We have some considerable concern with these releases since there is great danger that preliminary data might be used to draw conclusions contrary to the final outcome of the study. The potential for misleading the public is great and any way in which this potential could be minimized would seem to us to be highly desirable.

At the present time, clear-cut pathways for the clearance and release of formal reports have been established. Such reports would include reports of preliminary findings from carcinogenesis bioassay, summary reports of completed studies, and final technical reports. The first of these reports can be released when necessary and it would not place great demands on program resources; summary reports can be made available quickly upon completion of the histopathology and biostatistical analysis but do place significant demands on our program resources; completed technical reports require a proportionately longer period of time and commitment of program resources. The first completed technical report on bioassay results (Trichloroethylene—NCI Carcinogenesis Technical Report Series No. 2) has just been released. Since this has served as a prototype for all subsequent releases of this kind, it would be unfair to attempt to estimate the cost of such volumes based on this one. No feedback on the value of these reports is yet available but we anticipate that we will soon have considerable information on this question. We have already received requests for the translation of the first volume of the technical reports (Guidelines for Carcinogen Bioassay in Small Rodents—NCI Carcinogenesis Technical Report Series No. 1) into foreign languages.

CHRONOLOGY OF CARCINOGENS

Mr. OBEY. NCI has reported that 36 chemicals and chemical compounds are known human carcinogens. Substances in this list include asbestos, benzidine, tobacco smoke, and coke oven effluents. How long has the human carcinogenicity of these substances been known?

Dr. RAUSCHER. The following indicates the year each substance was "reported" or "recognized" as being carcinogenic to man. It must be stressed that in many of these cases, particularly where the substance specified is a poorly characterized mixture, the recognition of human carcinogenic hazard occurred gradually over a period of many years.

Substance	*First reported as human carcinogen*
Beta-naphthylamine	1954 (case reports since early 1900's).
Benzidine	1954 (case reports since 1930's).
4-aminobiphenyl	1955 (case reports since 1930's).
4-nitrobiphenyl	(Known to be metabolically converted to 4-amino-biphenyl).
Chlornaphazine	1964.
Mustard gas	1957.
Diethylstilbestrol	1971.
Bis(chloromethyl)ether	1973.
Vinyl chloride	1974.
Aflatoxin	1975.
Asbestos	1955 (case reports since 1930's).
Arsenicals	1947–57.
Chromates	1951.
Conjugated estrogens	1975.
Tobacco (chewing)	1933.
Tobacco smoke	1950.
Soots	1775.
Tars	1892.
Pitches	1892.
Asphalts	1947.
Cutting oils	1950.
Shale oils	1876.
Creosote oils	1924.
High boiling petroleum oils	1953.
Coke oven effluents	1974.
Various combustion products	1947.
Betel nut (chewing)	1959.
Radium [1]	1940's.
Thorotrast [1]	1940's.
Uranium ores [1] (radon and radon daughters)	1940's.
Other radioactive materials [1]	1940's.

[1] Carcinogenicity due to radiation.

In addition, certain manufacturing exposures have been clearly identified as showing evidence of carcinogenic effects in exposed people:

Substance	*Reported as human carcinogen*
Auramine	1954.
Magenta	1954.
Isopropyl oil	1959.
Wood dust	1975.
Nickel refining	1958.

REGULATORY ADEQUACY

Mr. OBEY. Is the regulation of these carcinogens adequate to protect the public?

Dr. RAUSCHER. Regulation of carcinogens, as well as other substances, depends upon a variety of factors that include legislative authority, social behavior, and regulatory and enforcement activities. It is now apparent that cigarette smoking is responsible for 30 percent of the cancer incidence in the United States, and yet it could hardly be argued that regulation is adequate to protect the public. In other instances, regulatory agencies are continuing to struggle to tighten regulations and to enforce those that already exist, in the hope of reducing the cancer burden attributable to specific carcinogenic agents. In some cases, it is readily possible to ban the offending agent and to end the problem attributable to that agent. In other cases, such as with vinyl chloride, the societal, economic, and health issues are far more complex. Indeed, our scientific tools often lack the capacity for providing precise information on risk and the imposed cancer burden thus requiring the application of judgment in regulatory decisions.

Mr. OBEY. What is NCI doing to encourage Federal regulation of these carcinogens?

Dr. RAUSCHER. NCI is increasing its efforts to foster understanding of the hazards attendant to exposure of carcinogens. It must be recognized, however, that many scientific questions of vital importance to public health issues remain unanswered and that effective regulation in the interest of public health depends upon two kinds of specialized knowledge: one relates to the scientific state of the art, and the other to the total nature of the regulatory problem. It is, therefore, essential in the interest of public health that NCI work closely with the Federal regulatory and enforcement agencies. Within the past 18 months, we have increased significantly our level of effort in this area.

BIOASSAY DATA

Mr. OBEY. Could you for the record provide the committee with a listing of all the chemicals you have initiated bioassay tests on? Tell us how each chemical is commonly used, the date tests were initiated, the name of the contractor doing the tests and the date you expect to issue a report on the tests. If the tests on a particular chemical have progressed far enough, tell us the date the animals were sacrificed, the date the pathology was completed and the date the final report was completed. If as much as a year has elapsed between the time the animals were sacrificed and no report has been issued, please provide for the record an explanation of why such a delay is taking place.

Dr. RAUSCHER. We are preparing a list of chemicals subjected to bioassay tests. The list as well as the associated information requested will require approximately 2 weeks to compile. As the information is compiled we will promptly provide it to the committee.

VIRAL CLUSTERS

Mr. OBEY. A scientist named Dr. Nathan Mantel in your field studies and statistics program did a paper a few years ago concerning the incidence of viral clusters as a random process. CDC has been working under contract with your virology program to prove a correlation between the clusters and natural viral exposures, but I understand that Dr. Mantel says that you could predict that clusters would occur on simply a random basis. Could you submit a short summary of Dr. Mantel's paper?

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Dr. RAUSCHER. Many articles have been written relevant to viral clusters as a random process, and I assume the one you are referring to is entitled "Time-Space Clustering of Childhood Leukemia in New Zealand," which appeared in the journal of the National Cancer Institute in 1971. In this study we evaluated the extent to which cases of this disease cluster in time and space in order to shed light on the possible viral etiology of childhood leukemia. The sample consisted of New Zealand children with leukemia diagnosed before their 15th birthday. The date of diagnosis and the home address were the time and space coordinates used in two statistical procedures, developed by Knox and Mantel. Statistically significant time-space clustering was noted in children less than 6 years old at diagnosis, but clustering was quite low in children at other ages. When the analysis was confined to successive 6-year periods or an intermediate 6-year period, rather than the entire 12 years of the study, evidence of clustering diminished noticeably. This suggests the effect of extraneous factors on the statistical procedures used. The marked growth of New Zealand and major population shifts from urban and suburban areas may have had an important and unpredictable role in this analysis. In the epidemiology of leukemia, growth and mobility of the study population must be considered as possible confounding variables whenever time-space clustering is detected.

CANCER CONTROL DIVISION

Mr. OBEY. Can you tell us for the record what the Division of Cancer Control does?

Dr. RAUSCHER. The Division of Cancer Control and Rehabilitation plans, directs, and coordinates an integrated program of cancer control and rehabilitation activities with the goal of identifying, testing, evaluating, demonstrating, communicating, and promoting the widespread application of available and new methods for reducing the incidence, morbidity, and mortality from cancer. The division serves as the nucleus of a coordinated national effort to control cancer, involving all appropriate elements of the Department of Health, Education, and Welfare, other Federal agencies, State and local health departments, voluntary health agencies, and other elements of the private health community.

In collaboration with the research divisions of the National Cancer Institute, the Division of Cancer Control and Rehabilitation identifies candidate control techniques and methods for inclusion in the field test and demonstration activities in limited community settings. The division also serves as the focal point in the National Cancer Institute for research in cancer rehabilitation.

The division also advises the Institute Director on program-related aspects of grants and contracts and participates in their evaluation as they relate to cancer control and rehabilitation.

Mr. FLOOD. Mr. Roybal.

NCI BUDGET CUTBACK

Mr. ROYBAL. Last year the National Cancer Institute received an appropriation of $743 million. At that time, you testified that you needed all the money to carry on necessary research. Now you are here saying

$687 million is enough for this year. Did we give you too much last year?

Dr. RAUSCHER. No, sir. I still feel strongly that we have effectively and efficiently obligated the funds which the Congress had provided last year. I further think that we do have the scientific base available where we could, in fact, effectively have utilized more funds last year.

Mr. ROYBAL. What programs will have to cut back this year due to a cutback in funding?

Dr. RAUSCHER. Research that would be adversely affected would include:

We could not continue to expand the development of the necessary documentation on the evaluation of carcinogenic risks to man. We would have to reduce not only the number of chemicals being screened for carcinogenicity, but also reduce research into improving the methods by which we screen these chemicals.

The cancer centers program which is already receiving less than recommended levels of support in fiscal year 1976 will continue to be funded at levels considerably less than recommended by the National Cancer Advisory Board. No new centers could be initiated.

In our task force programs, both the breast cancer and pancreatic cancer research efforts would be adversely affected. Efforts in breast cancer research have been highly productive and the new research emphasis to reduce tumor spread, which has great potential, will have to be limited. Pancreatic cancer is the fourth leading cancer killer in man. Research on this organ site needs to be expanded but efforts would be delayed at the reduced funding level in fiscal year 1977.

There will be no new awards in the clinical cooperative groups and the funding of competing renewals would be approximately 25 percent below the approved levels. This program would not have the capacity to utilize the full range of modalities of surgery, radiation, chemotherapy, and immunotherapy. This is critical because the use of these combinations has been shown to be effective in the treatment of many cancers, such as breast cancer.

The Institute will be able to fund 10.3 percent of National Cancer Advisory Board approved competing regular research grants. This compares to a 1976 level of 46.4 percent.

The immunological aspects of cancer research as well as the combined modality treatment aspects will not be supported at a level consistent with the research base available for exploitation.

While the cancer control aspects of the program will continue to receive high priority, the impact of the current fiscal year 1977 budget level will undoubtedly deter and hinder its progress.

Mr. ROYBAL. How will this affect our overall effort in the fight against cancer?

Dr. RAUSCHER. The impact of $687 million level in fiscal year 1977 which is $74.3 million below the 1976 level would result in a serious slowdown in the momentum of the National Cancer Institute program. No programs will be deleted, but there will be reduced levels in all programs resulting in the termination of projects and reduction in the number of awards.

Mr. ROYBAL. Will any people have to be laid off as a result of the budget cuts? If so, how many people?

Dr. RAUSCHER. Regarding positions, in fiscal year 1976 we are anticipating receiving the total positions alocation by the Congress, that

is 1,968 positions. The fiscal year 1977 budget request contains 1,887 positions. I would hope that through congressional action during the appropriations process that the personnel strength not be reduced below the 1976 level. However, if the Institute's ceiling were to be reduced near the beginning of fiscal year 1977, the reduction of 81 positions would hopefully be accomplished through attrition so that by the end of the fiscal year the Institute would be down to its personnel ceiling. However, should such a reduction come near the end of the fiscal year, then it is possible some personnel may have to be laid off. Also, an $83 million reduction in our grants and contracts operation could have an adverse effect in personnel supported by the awards. It would be extremely difficult to accurately project how many people would be laid off since the organizations which employ them may be able to shift their talents to other research projects for which they have support. In any event the number of personnel supported by contract or grant awards of the National Cancer program would be reduced. I would estimate that a reduction of $83 million would result in reducing the number of individuals supported by NCI by approximately 3,000.

CANCER DRUG MARKETING

Mr. ROYBAL. You indicate that you have developed some drugs that are now being used in the fight against cancer. Who markets these drugs?

Dr. RAUSCHER. The drugs developed through the collaborative research activities of the NCI Drug Development program which have established usefulness against cancer are marketed by the pharmaceutical industry. The pharmaceutical industry is involved in the research and development of cancer drugs as well as the marketing of cancer drugs developed by the National Cancer Institute.

Mr. ROYBAL. If the large pharmaceutical companies do the marketing, why should they profit from the Government's research?

Dr. RAUSCHER. Drug development in the cancer field is not a highly profitable area which explains why the Federal Government has been so heavily involved in the research and development aspect since the mid 1950's. The potential commercial market for such drugs is minuscule in comparison to the market for a pain killer, tranquilizer, vitamin or an anti-infective therapy. To take a drug which has been shown to have value in cancer therapy and make it available to the entire American public requires the marketing potential of a pharmaceutical company. The National Cancer Institute does not have the resources to undertake marketing its own drugs. The pharmaceutical companies enable the NCI to smoothly and rapidly get the drugs it successfully develops out to the entire public where they can have their maximum impact in the improvement of patient care.

The pharmaceutical companies chosen to market NCI drugs are picked through a competitive peer review process identical to a contract review. A request for proposal (RFP) is prepared by NCI offering the clinical data on a drug in return for rapid and efficient marketing. The responses to the RFP are reviewed by a committee and a company chosen on the basis of their time frame for the marketing, commitment to marketing, postulated price, and potential ability to successfully undertake the project. In the past we have had many re-

sponses to each RFP. A contract is formally signed with the chosen company.

Mr. ROYBAL. Do they pay a royalty?

Dr. RAUSCHER. No, sir, no royalties are paid.

Mr. ROYBAL. If not, what reimbursement arrangement is used?

Dr. RAUSCHER. No money is exchanged in either direction. The NCI feels that it is an equal "trade-off." The pharmaceutical company recognizes some profit, while the Government has the advantage of getting drugs which have proven effective in cancer therapy to the public.

ENVIRONMENTAL CANCER CAUSES

Mr. ROYBAL. Let us suppose that the statement that cancer can be attributed to environmental factors is correct. Does that mean we have to dramatically alter our society in order to prevent cancer? If that is so, how will society be altered?

Dr. RAUSCHER. A pristine environment, totally and completely devoid of chemicals with potential to cause cancer, would necessarily impact profoundly upon the present structure of our society. However, an environment in which exposures to cancer-causing substances is effectively and intelligently controlled to reduce significantly current cancer burden attributable to such agents is feasible and may well be possible without severe societal effect. In order to address this task, it is necessary to develop and use an improved capability for assessing the qualitative and quantitative nature of the human response from exposure to potential cancer-causing substances.

It has been claimed that only a small percentage of total manmade chemicals are capable of producing cancer. On that basis, it can be argued that complete elimination of manmade cancer-causing substances would have little effect on the incidence and mortality of cancer.

It is important to note that chemical properties required for certain technological purposes are the same properties responsible for cancer induction—to completely eliminate these chemicals would require elimination of such dependent technologies and that tens of thousands, and perhaps hundreds of thousands of chemicals, including man made and natural, are considered potentially cancer-causing because of their chemical properties.

The challenge for the future will be to reduce the extent of human exposure to cancer-causing chemicals to levels consistent with dramatic reductions in the incidence of the disease, and to achieve this without undue and unnecessary economic and societal harm. The role of nutrition as it relates to cancer will have an impact on dietary habits of the populace. Occupational hazards in the workplace will, of necessity, need to be reduced.

Mr. ROYBAL. A few years ago there was a cyclamate scare. There were reports that it caused cancer. Now you have concluded it does not. Why did you take action without being sure that cyclamates did cause cancer?

Dr. RAUSCHER. There appears to be much confusion about the actions taken by the Food and Drug Administration with regard to cyclamate. At the time that legislation was brought into existence requiring that new food additives be extensively tested for adverse effects before being introduced into the environment, it was clear that one could not reasonably introduce a requirement that all food additives (even those which had been used extensively for long periods of time) be subjected

to such testing. Such tests would have been of monumental proportions.

As a result, many toxicologists were surveyed and from this survey was developed a list of materials which were "generally recognized as safe" (GRAS), and suitable for use without further testing. These materials comprised the well-known GRAS list and cyclamate was among them. When it was reported that certain studies suggested serious adverse effects for cyclamate administration, the Food and Drug Administration took the position that the substance could no longer be generally recognized as safe and should, therefore, require the same sort of evidence of its safety as other food additives do. Data were not available to provide such evidence, and cyclamate was simply removed from the list of the materials approved as being GRAS. A petition for the use of cyclamate as a food additive was only presented to FDA by the manufacturer several years later. It is still under review.

Mr. ROYBAL. If you had a reasonable belief, why did you act only against cyclamates? Aren't there other products which present a reasonable possibility of being cancer-producing, but that haven't been taken off the market?

Dr. RAUSCHER. Almost any product which has not been adequately tested for its carcinogenic potential presents a "reasonable possibility" of being cancer producing. Materials for which there is extensive human exposure are considered on a regular basis for inclusion in our testing program. Those having the highest priority (based on exposure as well as a number of other factors) are entered into the long term animal bioassay program. In the event that such materials show evidence of carcinogenic effects, the appropriate regulatory agencies are advised. The NCI does not have regulatory authority.

Mr. ROYBAL. How many businessmen were hurt by your action of taking cyclamates off the market?

Dr. RAUSCHER. It is very difficult to estimate the number of businessmen hurt when cyclamates were taken off the market. There are several industries which were affected adversely by the ban, that is, pharmaceutical, food and soft drink.

Mr. FLOOD. Mr. Shriver.

BUDGET REDUCTIONS

Mr. SHRIVER. Dr. Rauscher, when you take away items sent as rent, utilities, travel, printing, pay raises, and other inflation-caused increases, this budget request is actually more than $83 million lower than 1976, is it not? That's the actual cut in project contracts, grants, subsidies, and contributions shown on page 22 of the book.

Dr. RAUSCHER. Yes, Mr. Shriver; I think it is very valid to say that while the actual dollar reduction is $83 million the impact is greater than this. Also, the $83 million does not take into account the inflationary costs within contracts and grants. May I add, sir, that, as you know, this inflationary impact is equal to virtually all other programs in Health.

TOTAL ENVIRONMENTAL CANCER BUDGET

Mr. SHRIVER. You mention there are 20 Federal agencies and subagencies involved in one way or another in the field of environmental cancer activities. We can add to that the efforts of State and local governments, hospitals, universities, the American Cancer Society, and

other groups—not just in the environmental area, but all types of cancer. In addition to this request, can you estimate the total spent for all of these activities this year? That may be a large order, but has anyone come up with such an estimate?

Dr. RAUSCHER. Yes, Mr. Shriver, based on available published data, total expenditures in fiscal year 1976 for non-NCI supported cancer activities of all kinds are approximately $300 million. Of this total, approximately $70 million is expended for activities in environmental cancer of which approximately $40 million is for activities conducted by other Federal agencies and $30 million for activities conducted by non-Federal organizations. In summary, the total estimated cost of cancer research in this country is $1 billion ($0.7 billion through NCI funding and $0.3 billion from all other U.S. sources).

Mr. SHRIVER. On the other side of the coin, can you estimate how much this Nation loses due to cancer? We certainly can't measure the human losses, but how about income loss, productivity loss, medical treatment expenditures, and other costs related to cancer?

Dr. RAUSCHER. In 1968 an estimate of 1.8 million work-years was calculated as being lost due to cancer mortality—work time lost while sick is not included in these figures.

Using this estimate as a base economic losses due to cancer can be estimated as follows: Assuming an average annual wage of $10,000 and 1.8 million work-years lost annually, we estimate a loss of $18 billion per year of productive income in the United States. Annual medical costs for cancer patients are estimated to be at least $3 billion, bringing the annual total cost to $21 billion. This figure is considered to be conservative because of the time period of the base estimate.

CANCER ACCOMPLISHMENTS

Mr. SHRIVER. You are submitting, according to your statement, a list of accomplishments of the national cancer program. Could you mention just a few of those this morning?

Dr. RAUSCHER. Yes, sir, I have submitted a list of accomplishments of the national cancer program and am pleased to highlight some of them for you. They are as follows:

A study of the treatment of breast cancer with less radical surgery has shown to date that it may be as effective as radical surgery. If the trend continues, the results will lead to treatment tailored to the individual patient and in many cases significantly different from the traditional radical surgery.

More than 50 percent of children with acute childhood leukemia treated at various centers in the Nation now survive more than 5 years without disease.

It is firmly established that chemotherapy—drug treatment—combined with surgery and radiotherapy is curative in 80 to 90 percent of patients with Wilms' tumor, a previously fatal childhood cancer of the kidney.

A nationwide breast cancer detection demonstration program encompassing 27 projects is underway in 25 States. Some 230,000 women have been examined and 4,000 biopsies have been reported. Of these, about 800 have been determined to be cancer. About 77 percent of confirmed cancers had not spread, a condition crucial to increased survival; this compares well to the 45–50 percent of patients diagnosed

with localized cancer in the usual medical practice. About 40 percent of the cancers were detected by the technique of mammography—X-ray—alone.

Use of an improved fiberoptic endoscope, a flexible instrument that permits determination of the location and extent of the tumor, is assisting the detection of cancer of the colon in earlier stages. The instrument is also proving valuable in the diagnosis of cancer of the pancreas.

New chemicals found to be carcinogenic include vinyl chloride, chlordane, trichloroethylene, ethylene dibromide, heptachlor, DES, and kepone.

A system has been developed for ranking thousands of chemicals for their estimated risk for carcinogenic potential. This information will help use the bioassay test resources most efficiently, and will also provide early guidelines to the chemical industry as to the potential hazard of a new chemical compound about to be introduced into the environment.

The new SEER program—surveillance, epidemiology, and end results reporting—is monitoring the trends in cancer incidence, changes in diagnostic and treatment priorities, and associated survival rates of cancer patients. This program will provide continually updated information on cancer statistics in the United States and will therefore serve as a direct check on how well—or how badly—we are doing.

International collaboration in cancer as directed under the National Cancer Act includes formal agreements with the Governments of the U.S.S.R., Japan, and Poland, and additional cooperative projects in more than 20 countries. Effective coordination and cooperation have been achieved with the World Health Organization, the International Union Against Cancer, and other international organizations concerned with cancer. The results of our international activities are expected to benefit the American people as well as peoples throughout the world.

Mr. SHRIVER. How many years will it be before you will have new national survival figures which can be attributed to the national cancer program?

Dr. RAUSCHER. It can take a minimum of 10 to 15 years for some of the research results generated by the expanded cancer program to be reflected in benefit for most people. A clinical therapeutic trial serves as useful model for illustrating this delay. The trial itself may take as long as 5 years to complete. It may take an additional 3 to 5 years to confirm favorable results. This phase may be concurrent with dissemination of results via professional and public education. The new therapeutic procedures must then be put into general practice and time must elapse to provide for newly diagnosed and treated patients to be followed for 1, 3, or 5 years and for the results to be reported from population-based cancer registries to the NCI.

The cancer surveillance, epidemiology and end results (SEER) program is designed to provide information on cancer incidence and patient survival. Nine population-based cancer registries are reporting all newly diagnosed cancers identified in their respective populations, compositely representing approximately 10 percent of the U.S. population.

Data from this program will be summarized annually for the most frequently occurring cancers and for the total of all cancers. Inci-

dence data will be available with a lag of 12 months after the close of a calendar year and 1-year survival results will of necessity require a lag of at least 24 months. Thus, 1-year survival results for cases diagnosed during 1973 will be available early this year (1976); 3-year survival results accordingly must await 4-plus years after the close of calendar year for reporting.

CONSTRUCTION

Mr. SHRIVER. What are the construction items you show in the tables? I see $25 million for 1976, and $10,339,000 for 1977.

Dr. RAUSCHER. In 1976, $20 million of the $25 million will be used to fund construction grants for projects at various institutions across the country including $6.5 million earmarked for the Sidney Farber Cancer Center in Boston, Mass. The remaining $5 million will be for modernization and renovation on facilities on the NIH campus, the Frederick Cancer Research Center, and other Federal facilities.

The $10,339,000 requested in fiscal year 1977 will enable us to fund $7.3 million for the modernization and renovation of space for cancer research as well as construction grants for the construction of biohazard facilities; $3 million will be used for the construction, renovation, and modernization of space on the NIH campus, at the Frederick Cancer Research Center and other Federal facilities.

TREATMENT CUTS

Mr. SHRIVER. There is a $22 million cut proposed in the area of treatment research. What specific projects would that effect?

Dr. RAUSCHER. Significant progress has been made in clinical treatment research as well as closely related efforts. The combined modality approach to treatment which has been so successful in breast cancer recently is an approach which can be applied to all types of cancer. A $22 million cut in treatment research would diminish our ability to exploit present research opportunities relating to the treatment of tumors such as colon cancer, ovarian cancer, prostatic cancer, head and neck cancer, pancreas cancer, stomach cancer and others. It would diminish the ability to support the research so essential to continuing to develop the new ideas and leads which feed into the successful application of the combined modality thrust. This includes the development and testing of new drugs, new immunotherapeutic manipulations, new radiation therapy delivery systems and new applications of surgical oncologic research.

The treatment research program has brought many of the fundamental basic science advances into juxtaposition with clinical research for practical application. Any reduction in the current growth will most assuredly result in a loss of the momentum and progress of the overall research program.

POSITIONS

Mr. SHRIVER. In our report last year, this committee urged you to work on your manpower shortage so that there would be sufficient positions to manage the national cancer program. The book states that you have added 71 positions. Do you consider that sufficient to manage the program?

Dr. RAUSCHER. The 71 positions have been added as a result of the action in the 1975 appropriation. An additional 79 positions are about to be released to NCI which are included with the 1976 appropriation. They will give us a full-time ceiling of 1,968. The NCI has developed work measurement and manpower forecasting systems to provide some basis for quantifying staff needs. These work measurement systems are based on estimated program activities which will result from the funds which are made available to the NCI. In preparing for the fiscal year 1976 budget these systems indicated that 2,115 positions would be required to administer a budget of $786 million. Since the final budget was less than this, by extrapolation we believe that 2,084 positions would be needed.

CYCLAMATES

Mr. SHRIVER. You are really getting involved in the environmental field, and that is good. I am interested in the story on cyclamates, however new research appears to be reversing the earlier decision banning that product. Was there insufficient research prior to that FDA ban?

Dr. RAUSCHER. There appears to be much confusion about the actions taken by the Food and Drug Administration with regard to cyclamate. At the time that legislation was brought into existence requiring that new food additives be extensively tested for adverse effects before being introduced into the environment, it was clear that one could not reasonably introduce a requirement that all food additives, even those which had been used extensively for long periods of time, be subjected to such testing. Such tests would have been of monumental proportions.

As a result, many toxicologists were surveyed and from this survey was developed a list of materials which were generally recognized as safe [GRAS], and suitable for use without further testing. These materials comprised the well-known GRAS list and cyclamate was among them. When it was reported that certain studies suggested serious adverse effects from cyclamate intake in animals, the Department—Food and Drug Administration—took the position that the substance could no longer be generally recognized as safe and should, therefore, require the same sort of evidence of its safety as required of other food additives. Data were not available to provide such evidence, and cyclamate was removed from the list of the materials approved as being GRAS. A petition for the use of cyclamates as food additives was presented to FDA by the manufacturer several years later and it is under review. As part of that review, the Committee of FDA requested that the NCI undertake an evaluation of all data on the carcinogenicity of cyclamate. A committee of outside experts and NCI staff undertook this task and the principal findings are as follows: The committee concludes that the present evidence does not establish the carcinogenicity of cyclamate or its principal metabolite, cyclohexylamine, in experimental animals. No conclusion could be reached concerning the question of cyclamate's potential carcinogenicity in humans due to the short post-exposure observation time, the insensitivity of epidemiologic studies to detect relatively small changes in cancer incidence, and other factors.

The committee expresses concern over the statistically significant increase in tumors in cyclamate-treated animals from several studies;

however, the interpretation of these results is confounded by the nature of the test procedures for animal strain employed. The presence of tumors of the urinary tract in other animal studies, though not in statistically significant numbers, is cause for additional concern.

The committee notes the relatively limited sensitivity of current bioassay systems. Although no chemical can be proven unequivocally to lack carcinogenicity with these systems, ones with a significant carcinogenic hazard for humans could escape detection.

Mr. SHRIVER. Would you furnish for the record the location of the 17 comprehensive cancer centers?

Dr. RAUSCHER. Yes; I shall be happy to do this for the record. To date, we have identified 17 comprehensive cancer centers which we will be happy to submit for the record.

COMPREHENSIVE CANCER CENTERS

1. Memorial Sloan-Kettering Cancer Center, New York, N.Y.
2. The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Tex.
3. University of Wisconsin, Wisconsin Clinical Cancer Center, Madison, Wis.
4. Roswell Park Memorial Institute, Buffalo, N.Y.
5. Fred Hutchinson Cancer Research Center (affiliated with the University of Washington), Seattle, Wash.
6. Sidney Farber Cancer Center, Boston, Mass.
7. University of Alabama, Cancer Research and Training Center, University of Alabama, Birmingham, Ala.
8. Johns Hopkins University Comprehensive Cancer Center, Baltimore, Md.
9. Duke University, Duke University Medical Center, Durham, N.C.
10. University of Southern California, LAC–USC Cancer Center, Los Angeles, Calif.
11. Comprehensive Cancer Center of Greater Miami, Miami, Fla.
12. Mayo Comprehensive Cancer Center, Mayo Clinic, Rochester, Minn.
13. Yale University Cancer Research Center, Yale University School of Medicine, New Haven, Conn.
14. Colorado Regional Cancer Center, Inc., Denver, Colo.
15. Illinois Cancer Council which includes: Rush-Presbyterian-St. Lukes Hospital, Chicago, Ill., and the University of Chicago Cancer Center, the University of Chicago, Chicago, Ill., and Northwestern University Cancer Center, Northwestern University School of Medicine, Chicago, Ill., Illinois Department of Public Health.
16. Georgetown University Hospital, the Vincent T. Lombardi Cancer Research Center, Washington, D.C., and Howard University Cancer Research Center, College of Medicine, Washington, D.C.
17. The Fox Chase Cancer Center, Philadelphia, Pa., and University of Pennsylvania Cancer Center, School of Medicine, Philadelphia, Pa.

Mr. SHRIVER. Is the University of Kansas a comprehensive cancer center?

Dr. RAUSCHER. The University of Kansas is not a comprehensive cancer center. However, the university, through Dr. James Lowman, director of the University of Kansas Cancer Center, has indicated the intention of the cancer center and the university to develop a

comprehensive cancer center in Kansas City under the auspices of the university. Currently under Dr. Lowman's able leadership good progress is being made in developing a truly multidisciplinary center of high quality.

BASIC RESEARCH

Mr. SHRIVER. You said in your statement that the best course to follow at present is to invest about half of your funds in basic research. How did you reach that conclusion?

Dr. RAUSCHER. The program balance and priorities among the research thrusts and the intervention areas of cancer control are based on the recommendations of advisory groups, composed of leading cancer experts working in concert with NCI staff. With the development of the national cancer program 250 qualified scientists participated in numerous planning and review meetings and developed the national cancer plan. Emanating from these sessions come program priorities and program balances for the national cancer program.

The conclusion to invest about half of our funds in basic research is based on the nature of the biomedical research and development process, which encompasses a broad spectrum of activities ranging all the way from very fundamental research through developmental and applied research to the point at which a "practice-ready" technique or material is made available for use in appropriate patients or population groups. There is much that remains unknown about such basic processes as the structure and function of normal and neoplastic cells; the mechanisms of action of chemicals that induce cancer or at the other extreme, halt the cancer process; the nature of immune mechanisms. The information derived from basic research generally cannot be translated into measures which directly benefit cancer patients or potential patients. However, such information constitutes the raw material from which new ideas, new approaches, new drugs, and new technology are deliberately crafted and ultimately directed against well identified practical cancer problems. The idea of keeping the whole train of research and development events moving is more important than the concept of investing a fixed share of available funds in basic research. At present the NCI supports research in most facets of basic research and the 50-percent figure seems about right. It is quite possible that in response to changing needs and opportunities the figure may be adjusted up or down.

INTERNATIONAL RESEARCH

Mr. SHRIVER. Would you give us some examples of joint research projects which you carry out with other countries? How are these funded?

Dr. RAUSCHER. One example of joint research projects between NCI and other countries are the contracts between the NCI operating divisions and foreign scientists and institutions for specific research in areas where foreign expertise is acknowledged, for example, in cancer immunotherapy, epidemiology and other areas.

Through our bilateral agreements with the Soviets, the Japanese, and others, joint projects are in effect in cancer treatment, cancer immunology, cancer virology, carcinogenesis, genetics related to cancer, cancer epidemiology and cancer control.

Other joint projects have been developed in cooperation with the WHO, the UICC and the IARC. For example, NCI actively participates in and partially supports a WHO project on the international classification of diseases, especially oncology. The UICC and NCI's ICRDB program jointly sponsor a scientist-to-scientist exchange program which enables cancer researchers to enhance their communication through laboratory visits for collaborative research, workshops for cancer problem review and research planning.

Mr. FLOOD. Mr. Conte?

CANCER MORTALITIES

Mr. CONTE. Could you provide us with a list of the leading death-producing cancers and the percentage of deaths each cancer is responsible for?

Dr. RAUSCHER. The following are the estimated 1976 cancer deaths by site, sex, and percentage of deaths each cancer is responsible for:

Site	Estimated deaths	Percentage
MALE		
Lung	65,200	32
Other digestive	35,800	18
Prostate	19,300	10
Leukemia and lymphomas	18,500	9
Colon and rectum	18,000	9
Urinary	11,100	5
Oral	5,900	3
Skin	2,900	1
All other	25,300	13
Total	202,000	100

Site	Estimated deaths	Percentage
FEMALE		
Breast	32,800	20
Other digestive	27,200	16
Colon and rectum	20,900	12
Lung	18,600	11
Leukemia and lymphomas	15,500	9
Uterus	11,000	7
Ovary	10,800	7
Urinary	5,500	3
Oral	2,400	1
Skin	2,100	1
All other	21,200	13
Total	168,000	100

SMOKING HAZARDS

Mr. CONTE. Do you still feel that smoking is the major cause of lung cancer?

Dr. RAUSCHER. Yes. Smokers as a group appear to have 10 times higher risk to develop lung cancer than nonsmokers. Ninety percent or more of all lung cancer is caused by smoking. People who stop smoking will gradually reduce the risk to develop lung cancer and in a period of approximately 10 years their risk will be the same as that of the nonsmoker.

Mr. CONTE. Have any new efforts been launched to curtail smoking?

Dr. RAUSCHER. Yes. Research is being conducted to develop drugs that may reduce the craving for smoking. It appears that nicotine itself, used as a drug, or drugs that mimic nicotine may be useful to reduce this craving.

Our cancer control program, in cooperation with the Center for Disease Control, is in the process of analyzing data and assessing the current problems associated with smoking. This assessment is expected to be completed within the next 6 months. At that time, we hope to have further information relative to smoking habits.

Mr. CONTE. What steps are being taken to identify environmental cancer-causing agents?

Dr. RAUSCHER. Research efforts to identify cancer-causing chemicals in the environment are being conducted under our bioassay screening program. There are appoximately 540 chemical compounds currently

under test including industrial chemicals, pesticides, food additives, and drugs. These tests, using small animals as models, are underway at more than 20 laboratories throughout the United States, including the Frederick Cancer Research Center. In addition, new methods, in vitro, for the rapid and less expensive testing in chemicals with cancer-causing activity are being actively developed and their validity is being assessed.

Our testing program is part of a more comprehensive research effort designed to identify environmental cancer-causing agents which include the development and definition of chemical models for cancer induction, particularly those specific for the major target organs; and chemical analytical methods for the detection of carcinogens in the environment, in humans, or in tissues.

Mr. CONTE. Could you indicate roughly the percentages of funds allocated between causation, detection, and treatment research?

Dr. RAUSCHER. In fiscal year 1976, 32.6 percent of the Institute's research funds were for Cause and Prevention Research, 7.8 percent for Detection and Diagnosis Research, and 39.3 percent for Treatment Research. In addition 20.3 percent was allocated for Cancer Biology. In fiscal year 1977, the relationship would be approximately the same as 1976.

Mr. CONTE. Last year I discussed with you the debate about whether there is too much emphasis on viral causes of cancer. Have there been any advances in this area that would indicate whether or not it is worth the emphasis?

Dr. RAUSCHER. Yes; there has been. Within the last 12 months, chemical substances directly related to those of known cancer-causing viruses of monkeys and apes have been found in normal and cancerous human cells. Sera of normal individuals and cancer patients also contain antibodies to these viral materials. The results suggest that viruses closely related to those found in nonhuman primates are common viruses of man and probably etiologically associated with human cancer.

While the search for definitive human cancer viruses continues, virologists have clearly shown that activation of latent or inherited viruses accompanies the action of chemical and physical agents; that is, environmental carcinogens. Thus, viruses constitute the most valuable tools that will lead us to an understanding of the processes involved in the conversion of normal cells to cancer cells. In fact, tumor virus vaccines can prevent the induction of some chemically induced tumors in animals and may thus provide a common means for controlling many cancers in people.

MANPOWER

Mr. CONTE. What is the scientific manpower situation as it regards cancer research?

Dr. RAUSCHER. A study by the National Academy of Sciences acknowledges the need for additional research manpower in the areas of carcinogenesis, chemotherapy, drug development, epidemiology, immunology, radiation oncology, tumor biology and viral oncology. Furthermore, there is a continuing demand in cancer research institutions for new trainees, and most trainees are offered new positions even before they complete their training. A Radiation Research Society study shows that current training does not provide needed replacements in

the field of radiation therapy and consequently does not begin to address the documented need for additional manpower. A similar study indicates that only 10 to 20 percent of the major universities have sufficient staff for investigative immunology and that 750 to 1,000 clinical immunologists are currently needed at hospitals and medical schools. The extension of the National Research Service Awards Act program will permit the Institute to continue to support training in the fundamental disciplines of cancer research. Training in these disciplines will provide investigators for the major areas of cancer research.

INTRAMURAL VERSUS EXTRAMURAL EFFORTS

Mr. CONTE. What is the ratio of your intramural and extramural research?

Dr. RAUSCHER. In fiscal year 1976, obligations for intramural research will approximate 13 percent of the NCI budget; about 87 percent of the budget will be spent for extramural research. This is a ratio of approximately 1 to 7, intramural to extramural.

Mr. CONTE. The research manpower development program is significantly lower this year. How will this affect the work of the Institute?

Dr. RAUSCHER. Most of the reduction in manpower programs is a result of a reduction in our cancer clinical education program. This is a program whereby resources are provided for the improvement and expansion of cancer teaching at the undergraduate and graduate levels in schools of medicine, dentistry, osteopathy, public health, in major hospitals affiliated with medical schools and in specialized cancer institutions.

There is a continuing need to replace scientists leaving active investigator roles across the Nation and to provide fresh approaches and the enthusiasm that young investigators bring to their professions. With the proposed fiscal year 1977 budget, NCI would support 51 cancer clinical education grants as compared to 91 for fiscal year 1976.

Mr. CONTE. Have any significant developments been brought to your attention from outside the United States? Are you actively watching the programs in other nations?

Dr. RAUSCHER. Significant developments from outside the United States of America, such as the recent CMF mode of chemothreapy for breast cancer, are brought to the attention of NCI through grants and contracts of NCI's operating divisions and NCI's Office of International Affairs. The CMF mode of therapy combines the anticancer drugs—cyclophosphamide, methotrexate and 5-fluorouracil—and was developed by personnel in the National Tumor Institute in Milan, Italy, under partial NCI support. The use of CMF following surgery prevented recurrence of breast cancer in 94.7 percent of the women treated.

Another development of which we might have leearned only secondhand, had it not been for our U.S.-U.S.S.R. agreement, is the recent agreement reached between Bristol-Myers and the U.S.S.R. for "the exchange, acquisition or transfer of methods, processes, know-how and licenses, for the manufacture of products such as anticancer drugs, antibiotics, and nonnarcotic analgesics."

We are able to maintain an active overview of cancer programs in other nations through the bilateral agreements we implement through our interaction with international organizations and by our participa-

tion in international congresses, meetings and conferences. For example, our collaboration with the Soviets keeps us reasonably abreast of what is going on in the U.S.S.R. and, to an extent, in the Comecon or Soviet satellite nations. Our relationship with the Polish Peoples Republic adds a measure to the latter. NCI's agreement with the Japan Society for the Promotion of Science provides us with input in that geographic area of the world. Our European relationship is maintained primarily through grants and contracts; for example, with the National Institute of Health and Medical Research (Inserm) in France and agreements with our European countries.

Perhaps our most significant means of communication with foreign countries is being provided by our International Cancer Research Data Bank (ICRDB) which is almost fully operational. The functional elements of the ICRDB are constantly screening and abstracting approximately 1,000 foreign biomedical journals for cancer or cancer-related information. The foreign cancer information along with U.S.-generated data is computerizeed and by means of Cancerline in the National Library of Medicine Information Network is made available to domestic and foreign users.

Our relationship with the World Health Organizations (WHO), the International Union Against Cancer (UICC), the International Agency for Research on Cancer (IARC) and the European Organization for Research on the Treatment of Cancer (EORTC), enables us to maintain a continuing awareness of the most significant developments in cancer research and treatment throughout the world.

Mr. FLOOD. Mr. Patten.

NEW JERSEY CANCER CENTER

Mr. PATTEN. Recently, I shared the great shock of the people of New Jersey to learn that the State held the dubious distinction of ranking as one of the highest areas of cancer mortality.

A study issued by the National Cancer Institute revealed that cancer of the colon and rectum as well as of the esophagus, larynx, mouth and throat was found to be very high in north New Jersey and other urban areas. The Cancer Institute of New Jersey listed the State as having the highest mortality rate for rectal and bladder cancer and cancer of the ovary. All in all, it paints a very ugly picture.

There are indications that environmental and occupational factors play a major role in producing these startling figures. Of course, that is simply an assumption, though very much an educated assumption. This is why it is necessary that the Institute go beyond the reporting of these figures to determine or aid in determining why incidence of cancer mortality is so high in New Jersey and other Northeastern States.

The Cancer Institute of New Jersey is about to receive a major planning grant from the NCI and it is very much welcome because it is the start of an organized effort to consolidate all cancer programs and moneys in the State and to coordinate cancer research and reporting. I ask the NCI to continue to support the efforts of the Cancer Institute of New Jersey. The New Jersey institute has made a grant commitment and is currently looking for a qualified and eminent person to head its drive. I am very optimistic.

Mr. FLOOD. Thank you, Dr. Rauscher.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Amounts Available for Obligation[1/]

	1976 Estimate	1977
Appropriation	$743,564,000	$687,670,000
Request pending	18,163,000	---
Subtotal, adjusted appropriation	761,727,000	687,670,000
Comparable transfer to:		
"Department of State" (for transfer of shared administrative support of NCI overseas field station)	-23,000	---
Comparable transfer from:		
"Office of Director" (for transfer of Standard Level User Charge)	+943,000	---
Total, obligations	$762,647,000	$687,670,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 estimate - $81,000; 1977 - $81,000.

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National Cancer Institute

Budget Mechanism

	1976 Estimate			1977 Estimate		
	No.	FTE[1/]	Amount	No.	FTE[1/]	Amount
Research Grants						
Regular:						
Non-competing	1,526		$101,351,000	1,483		$112,844,000
Competing	655		56,380,000	177		21,551,000
Renewal	(243)		(20,248,000)	(123)		(13,250,000)
New	(412)		(24,388,000)	(54)		(3,829,000)
Supplemental	(223)		(11,744,000)	(176)		(4,472,000)
Subtotal	2,181		157,731,000	1,660		134,395,000
Specials:						
Cancer research centers	194		122,612,000	175		118,249,000
Task forces	158		14,100,000	130		12,600,000
Research career program	139	139	3,240,000	124	124	2,900,000
Clinical education program	91		8,492,000	51		5,000,000
Radiation development program	17		4,000,000	17		4,000,000
Cancer research emphasis grants	59		4,267,000	87		6,167,000
Subtotal	658	139	156,711,000	584	124	148,916,000
Total research grants	2,839	139	314,442,000	2,244	124	283,311,000

National Cancer Institute

Budget Mechanism

	1976 Estimate			1977 Estimate		
	No.	FTE[1/]	Amount	No.	FTE[1/]	Amount
Fellowships						
Non-competing	291	779	11,974,000	269	836	14,278,000
Competing	39	39	866,000	129	129	2,121,000
Renewal	(---)		(---)	(---)		(---)
New	(39)	(39)	(434,000)	(129)	(129)	(1,593,000)
Supplemental	(146)		(432,000)	(176)		(528,000)
Subtotal	330	818	12,840,000	398	965	16,399,000
Training grants						
Non-competing	46	374	5,323,000	14	106	1,764,000
Competing	---		---	---		---
Renewal	(---)		(---)	(---)		(---)
New	(---)		(---)	(---)		(---)
Supplemental	(---)		(---)	(---)		(---)
Subtotal	46	374	5,323,000	14	106	1,764,000
Research and development contracts	969		213,173,000	796		181,384,000
Intramural research and direct operations			127,789,000			134,447,000
Program management			6,331,000			7,415,000
Cancer control			56,806,000			51,386,000
Construction			25,000,000			10,339,000
Standard level user charge			943,000			1,225,000
TOTAL			762,647,000			687,670,000

1/ Full-time equivalents

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1977 JUSTIFICATION

National Cancer Institute
(In thousands of dollars)

Program	Research Grants			Training Programs		Research and Development Contracts	Intramural Research and Direct Operations	Program Management	Cancer Control	Construction	Total
	Regular Program	Specials: Cancer Centers	Specials: Other	Grants	Fellowships						
1976 Estimate											
A. Research											
1. Cause and prevention research	$33,330	$15,280	$10,310			$103,785	$34,868	$1,964			$199,537
2. Detection and diagnosis research	5,641	3,469	3,736			21,967	12,571	715			48,099
3. Treatment research	69,152	39,606	8,171			74,317	47,499	1,990			240,735
4. Cancer biology	49,608	30,588	150			13,104	29,613	1,207			124,270
Subtotal	157,731	88,943	22,367			213,173	124,551	5,876			612,641
B. Resource Development											
1. Cancer centers support		33,669					721	45			34,435
2. Research manpower development			11,732	5,323	12,840		1,334	94			31,323
3. Construction							534	43		25,000	25,577
Subtotal		33,669	11,732	5,323	12,840		2,589	182		25,000	91,335
C. Cancer Control							1,592	273	56,806		58,671
Total Obligations	157,731	122,612	34,099	5,323	12,840	213,173	128,732	6,331	56,806	25,000	762,647

DHEW - National Institutes of Health

CROSSWALK - 1977 COLUMN 1977 JUSTIFICATION

National Cancer Institute
(In thousands of dollars)

Program	Research Grants			Training Programs		Research and Development Contracts	Intramural Research and Direct Operations	Program Management	Cancer Control	Construction	Total
	Regular Program	Specials: Cancer Centers	Specials: Other	Grants	Fellowships						
1977 Estimate											
A. Research											
1. Cause and prevention research	$28,981	$15,220	$11,464			$86,950	$36,669	$2,288			$181,572
2. Detection and diagnosis research	4,831	3,742	3,376			17,709	13,900	832			44,390
3. Treatment research	57,313	38,836	7,777			65,560	49,416	2,327			221,229
4. Cancer biology	43,270	29,026	150			11,165	31,062	1,398			116,071
Subtotal	134,395	86,824	22,767			181,384	131,047	6,845			563,262
B. Resource Development											
1. Cancer centers support		31,425					831	54			32,310
2. Research manpower development			7,900	1,764	16,399		1,574	121			27,758
3. Construction							518	50		10,339	10,907
Subtotal		31,425	7,900	1,764	16,399		2,923	225		10,339	70,975
C. Cancer Control							1,702	345	51,386		53,433
Total Obligations	134,395	118,249	30,667	1,764	16,399	181,384	135,672	7,415	51,386	10,339	687,670

Summary and Explanation of Changes

1976 Estimated Obligations	$762,647,000
1977 Estimated Obligations	687,670,000
Net change	-74,977,000

	1976 Base		Change from Base	
	No.	Amount	No.	Amount
Increases:				
A. Built-in:				
1. Annualization of 1975 pay increase	---	$3,300,000	---	+$1,180,000
2. Within-grade pay increases	---	56,000	---	+70,000
3. Bureau of Employees Compensation	---	70,000	---	+15,000
4. FTS rate increase	---	480,000	---	+100,000
5. Service and Supply Fund	---	2,600,000	---	+135,000
6. Travel rate increase	---	3,100,000	---	+323,000
7. Postage rate increase	---	1,200,000	---	+200,000
8. Standard level users charge	---	943,000	---	+282,000
9. Payment to NIH Management Fund	---	22,098,000	---	+2,226,000
Subtotal	---	33,847,000	---	+4,531,000
Cause & prevention research	(---)	(7,014,000)	(---)	(+996,000)
Detection & diagnosis research	(---)	(3,658,000)	(---)	(+964,000)
Treatment research	(---)	(12,494,000)	(---)	(+1,658,000)
Cancer biology	(---)	(8,851,000)	(---)	(+589,000)
Cancer centers support	(---)	(179,000)	(---)	(+19,000)
Research manpower development	(---)	(611,000)	(---)	(+138,000)
Construction	(---)	(124,000)	(---)	(+17,000)
Cancer control	(---)	(916,000)	(---)	(+150,000)
B. Program:				
1. Research grants - regular program				
a. Non-competing continuations converting from competing status	1,526	101,351,000	+594	+51,114,000
(1) Cause & prevention research	(358)	(22,558,000)	(+130)	(+9,766,000)
(2) Detection & diagnosis research	(60)	(3,792,000)	(+23)	(+1,676,000)
(3) Treatment research	(574)	(41,419,000)	(+246)	(+25,143,000)
(4) Cancer biology	(534)	(33,582,000)	(+195)	(+14,529,000)

Summary and Explanation of Changes--Continued

	1976 Base		Change from Base	
	No.	Amount	No.	Amount
b. Competing (new, continuations, and supplementals.....	655	56,380,000	+177	+21,551,000
(1) Cause & prevention research.....	(143)	(10,772,000)	(+29)	(+3,218,000)
(2) Detection & diagnosis research.....	(25)	(1,849,000)	(+5)	(+520,000)
(3) Treatment research.....	(271)	(27,733,000)	(+100)	(+12,957,000)
(4) Cancer biology.	(216)	(16,026,000)	(+43)	(+4,856,000)
2. Fellowships				
a. Non-competing continuations converting from competing status...	291	11,974,000	+74	+3,935,000
(1) Research manpower development..	(291)	(11,974,000)	(+74)	(+3,935,000)
b. Competing (new, continuations, and supplementals).....	39	866,000	+129	+2,121,000
(1) Research manpower development..	(39)	(866,000)	(+129)	(+2,121,000)
	Pos.	Amount	Pos.	Amount
3. Intramural laboratory & clinical research.....	455	19,141,000	-18	+1,625,000
a. Detection & diagnosis research...	(147)	(4,595,000)	(-6)	(+391,000)
b. Cancer biology.....	(308)	(14,546,000)	(-12)	(+1,234,000)
4. Collaborative research & support.....	1,028	46,694,000	-44	+1,867,000
a. Cause & prevention research.....	(485)	(19,479,000)	(-22)	(+1,234,000)
b. Detection & diagnosis research...	(43)	(1,492,000)	(-2)	(+110,000)
c. Treatment research.	(500)	(25,723,000)	(-20)	(+523,000)
5. Program management.....	69	5,801,000	-3	+1,004,000
a. Cause & prevention research.....	(21)	(1,911,000)	(-1)	(+301,000)
b. Detection & diagnosis research...	(7)	(664,000)	(---)	(+109,000)

Summary and Explanation of Changes--Continued

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
c. Treatment research.	(21)	(1,830,000)	(-1)	(+313,000)
d. Cancer biology.....	(13)	(1,092,000)	(-1)	(+174,000)
e. Cancer centers support.....	(1)	(35,000)	(---)	(+7,000)
f. Research manpower development.....	(1)	(80,000)	(---)	(+25,000)
g. Construction.....	(1)	(35,000)	(---)	(+6,000)
h. Cancer control.....	(4)	(254,000)	(---)	(+69,000)
Subtotal.....	1,552	242,207,000	-65	+83,217,000
Total, increases...				+87,748,000
Decreases:	No.	Amount	No.	Amount
A. Program:				
1. Research grants				
a. Non-competing completed or converted to competing status - regular program	---	---	-637	-39,621,000
(1) Cause & prevention research....	(---)	(---)	(-140)	(-6,561,000)
(2) Detection & diagnosis research....	(---)	(---)	(-25)	(-1,157,000)
(3) Treatment research....	(---)	(---)	(-262)	(-22,206,000)
(4) Cancer biology	(---)	(---)	(-210)	(-9,697,000)
b. Competing completed or converting to non-competing - regular program	---	---	-655	-56,380,000
(1) Cause & prevention research....	(---)	(---)	(-143)	(-10,772,000)
(2) Detection & diagnosis research....	(---)	(---)	(-25)	(-1,849,000)
(3) Treatment research....	(---)	(---)	(-271)	(-27,733,000)
(4) Cancer biology	(---)	(---)	(-216)	(-16,026,000)
c. Special programs....	658	156,711,000	-74	-7,795,000
(1) Cause and prevention research....	(148)	(25,590,000)	(+14)	(+1,094,000)
(2) Detection & diagnosis	(47)	(7,205,000)	(-7)	(-87,000)
(3) Treatment research....	(122)	(47,777,000)	(-7)	(-1,164,000)

Summary and Explanation of Changes--Continued

	1976 Base		Change from Base	
	No.	Amount	No.	Amount
(4) Cancer biology.	(47)	(30,738,000)	(---)	(-1,562,000)
(5) Cancer centers support.....	(64)	(33,669,000)	(-19)	(-2,244,000)
(6) Research manpower development..	(230)	(11,732,000)	(-55)	(-3,832,000)
2. Fellowships				
a. Non-competing completed or converted to competing status....	---	---	-96	-1,631,000
(1) Research manpower development...	(---)	(---)	(-96)	(-1,631,000)
b. Competing completed or converting to non-competing.....	---	---	-39	-866,000
(1) Research manpower development...	(---)	(---)	(-39)	(-866,000)
3. Training grants				
a. Non-competing completed or converted to competing status....	46	5,323,000	-32	-3,559,000
(1) Research manpower development...	(46)	(5,323,000)	(-32)	(-3,559,000)
4. Research and development contracts.....	---	213,173,000	---	-31,789,000
a. Cause & prevention research.....	(---)	(103,785,000)	(---)	(-16,835,000)
b. Detection & diagnosis research....	(---)	(21,967,000)	(---)	(-4,258,000)
c. Treatment research..	(---)	(74,317,000)	(---)	(-8,757,000)
d. Cancer biology.....	(---)	(13,104,000)	(---)	(-1,939,000)
	Pos.	Amount	Pos.	Amount
5. Research management & program services.....	365	29,931,000	-14	-932,000
a. Cause & prevention research.....	(101)	(8,528,000)	(-3)	(-406,000)
b. Detection & diagnosis research....	(29)	(2,877,000)	(-1)	(-128,000)
c. Treatment research..	(103)	(9,442,000)	(-4)	(-240,000)

Summary and Explanation of Changes--Continued

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
d. Cancer biology.....	(69)	(6,331,000)	(-2)	(-357,000)
e. Cancer centers support.....	(14)	(552,000)	(-1)	(+93,000)
f. Research manpower development.....	(15)	(737,000)	(-1)	(+104,000)
g. Construction.....	(12)	(418,000)	(-1)	(-32,000)
h. Cancer control.....	(22)	(1,046,000)	(-1)	(+34,000)
6. Construction.....	---	25,000,000	---	-14,661,000
7. Cancer control.....	51	56,455,000	-2	-5,491,000
Total, decreases.....	416	486,593,000	-16	-162,725,000
Total, net change.....	---	---	-81	-74,977,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Pos.	1976 Revised President's Budget Amount	1976 Appropriation Pos.	1976 Appropriation Amount	1977 Estimate Pos.	1977 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
32	Research								
	(a) Cause and Prevention Research..	581	$180,147,000	607	$199,537,000	581	$181,572,000	-26	-$17,965,000
	(b) Detection and Diagnosis Research.....	217	43,649,000	226	48,099,000	217	44,390,000	-9	-3,709,000
	(c) Treatment Research.....	599	217,093,000	624	240,735,000	599	221,229,000	-25	-19,506,000
	(d) Cancer Biology.....	375	112,168,000	390	124,270,000	375	116,071,000	-15	-8,199,000
43	Resource Development								
	(a) Cancer Centers Support.....	14	31,915,000	15	34,435,000	14	32,310,000	-1	-2,125,000
	(b) Research Manpower Development..	15	27,466,000	16	31,323,000	15	27,758,000	-1	-3,565,000
	(c) Construction.....	12	22,577,000	13	25,577,000	12	10,907,000	-1	-14,670,000
49	Cancer Control								
	(a) Cancer Control.....	74	53,299,000	77	58,671,000	74	53,433,000	-3	-5,238,000
	Total obligations.....1,887		688,314,000	1,968	762,647,000	1,887	687,670,000	-81	-74,977,000
	(Standard Level User Charge).....		(943,000)		(943,000)		(1,225,000)		(+282,000)

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	1,968	1,887	-81
Full-time equivalent of all other positions	250	300	+50
Average number of all employees	2,137	2,187	+50
Personnel compensation:			
Permanent positions	$34,598,000	$36,261,000	+$1,663,000
Positions other than permanent	3,863,000	4,950,000	+1,087,000
Other personnel compensation	1,490,000	1,684,000	+194,000
Subtotal, personnel compensation	39,951,000	42,895,000	+2,944,000
Personnel benefits	5,791,000	6,218,000	+427,000
Travel and transportation of persons	3,100,000	3,423,000	+323,000
Transportation of things	373,000	494,000	+121,000
Rent, communications and utilities	2,873,000	3,123,000	+250,000
Printing and reproduction	1,289,000	1,446,000	+157,000
Other services:			
Project contracts	264,762,000	223,288,000	-41,474,000
Payment to NIH Management Fund	23,041,000	25,549,000	+2,508,000
Other	35,927,000	36,127,000	+200,000
Supplies and materials	20,800,000	21,919,000	+1,119,000
Equipment	5,000,000	5,375,000	+375,000
Grants, subsidies and contributions	359,740,000	317,813,000	-41,927,000
Total obligations by object	762,647,000	687,670,000	-74,977,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1976 House Report	
Environmental Carcinogenesis	
1. The Committee understands the pervasive nature of the problem of environmental carcinogens and urges the NCI to dedicate a substantial effort to determination of cancer hazards in the general environment. The Committee directs the Cancer Institute to work closely with the National Institute for Occupational Safety and Health in that Institute's occupational carcinogenesis program. (page 24)	1. The importance of research in environmental carcinogenesis is recognized and the NCI expanded its research efforts in this area as well as emphasized its interagency coordination and cooperation. The NCI co-sponsored a conference on occupational carcinogenesis in Spring 1975, with the National Institute for Occupational Safety and Health. The NCI continues to collaborate in the research on environmental agents, such as has been done with asbestos and vinyl chloride.
Positions	
2. The Committee notes that a critical manpower shortage at the NCI continues to exist even though Congress has mandated that sufficient positions be provided to manage the National Cancer Program. (page 24)	2. Since the Appropriations Hearings, 71 additional positions have been provided to the National Cancer Institute.
1976 Senate Report	
Nutrition and Cancer	
1. The NCI should expand the recently initiated high priority nutrition program. (page 36) The National Cancer Act of 1971 as amended directs the Director of NCI to "Collect, analyze and disseminate information (including information respecting nutrition programs for cancer patients and the relationship between nutrition and cancer)..."	1. The NCI's Diet, Nutrition and Cancer Program, established in FY 1975, covers the relationship of nutrition to the causation as well as the therapy of cancer. Planning sessions with top scientists who specialize in nutrition and related fields have been held. A project is currently being implemented for the overall coordination of the nutrition program.
Positions	
2. The Committee was concerned about manpower shortages in the National Cancer Program and particularly in the lack of positions and beds in the Clinical Center for cancer research, and that funds be provided to support these positions. (page 38)	2. Some additional positions have been provided to the National Cancer Program and at the Clinical Center.

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1976 Senate Report	
Construction	
3. The Committee noted that $6 million should be provided for the completion of the Sidney Farber Cancer Center in Boston, Massachusetts. (page 38)	3. In November 1975, the National Cancer Advisory Board approved a request for an additional $6.5 million for the completion of the Sidney Farber Cancer Center. This project should be funded by the end of the third quarter, FY 1976.

Authorizing Legislation

Legislation	1977 Authorized	1977 Appropriation requested
Public Health Service Act:		
Section 301 - Research and Investigation.....		
Title IV, Part A -- National Cancer Institute.....	$1,073,500,000	$669,507,000
Section 409 (b) -- Cancer Control.....	(88,500,000)	
Section 410C. -- Research.....	(985,000,000)	
Title IV, Part I -- National Research Service Awards.....	1/	18,163,000 2/

1/ Authorization expired June 30, 1975: extension legislation is pending.

2/ Funding estimate only. Total appropriation requested for this Institute is $687,670,000.

National Cancer Institute

(Comparable)

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	427,422,000	485,505,000	485,505,000	485,505,000 1/
1974	500,800,000	523,183,000	580,800,000	528,286,000 2/
1975	600,882,000	480,388,000 3/	755,882,000	692,548,000
1976	605,920,000	704,484,000	804,484,000	
Items Not Considered		(18,163,000)	(18,163,000)	
1977	687,670,000			

The figures presented in this table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of general research support grants is no longer the function of this institute. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes.

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 as authorized by Public Law 93-192.

3/ Excludes contracts not considered by House due to lack of authorization.

National Cancer Institute

(Actual)

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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 1/
1975	600,000,000	479,506,000 2/	755,000,000	691,666,000
1976	605,000,000	703,564,000	803,564,000	
Items Not Considered		(18,163,000)	(18,163,000)	
1977	687,670,000			

1/ Appropriation after reduction as authorized by Public Law 93-192.

2/ Excludes contracts not considered by House due to lack of authorization.

Justification

National Cancer Institute

	1976 Estimate		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Research	1,847	$612,641,000	1,772	$563,262,000	-75	-$49,379,000
Resource Development	44	91,335,000	41	70,975,000	-3	-20,360,000
Cancer Control	77	58,671,000	74	53,433,000	-3	-5,238,000
Total	1,968	762,647,000	1,887	687,670,000	-81	-74,977,000

General Statement

The scope of the National Cancer Program, as delineated in the National Cancer Act of 1971 is to "...plan and develop an expanded, intensified, and coordinated cancer research program encompassing the programs of the National Cancer Institute, related programs of other research institutes, and other Federal and non-Federal programs." (National Cancer Act, Section 407.(b) (1).) The National Cancer Program (NCP) was promulgated to conduct a nationally coordinated effort to achieve the conquest of cancer. The goal of the NCP is to develop the means to significantly reduce the incidence, morbidity and mortality of cancer in man and ultimately to develop the means to eliminate all human cancers.

Cancer research involves many organizations throughout the world. The greatest share of financial support for U.S. organizations and some support for non-U.S. organizations comes from the National Cancer Institute acting as the Federal agency responsible for the implementation and coordination of the NCP. A full range of research efforts is directed toward developing the means, the knowledge and the techniques needed to control or eliminate the disease. These efforts are organized around the research thrusts of cause and prevention, detection and diagnosis, treatment, and cancer biology, as well as, resource development and cancer control efforts.

Program balance and priorities among the research thrusts and the intervention areas of cancer control are based on the recommendations of advisory groups, composed of leading cancer experts in the United States, working in concert with NCI staff. Consideration of new opportunities and on-going programs is of major significance in determining related emphasis and priority of specific programs. Reallocation of resources and selection of new initiatives are based on "trade-offs" after considering the recommendations and decisions of the advisory groups and NCI staff. An example of a "trade-off" is the decision to emphasize research in combined modality therapy while maintaining drug development at a relatively constant level. Program balance results from this kind of "trade-off" between sustained effort in continuing research programs and identified opportunities for new research emphasis. The program balance and priorities reflected in this budget are a result of continued analyses of these alternatives.

A National Cancer Program Plan (NCPP) has evolved from efforts of leading cancer experts throughout the United States and the various subcommittees of the National Cancer Advisory Board. As a result of the continuous planning process within the National Cancer Plan, a series of recommendations for research and control activities were formulated by the scientific community and are organized in terms of major objectives for the Program. The research objectives are organized into the major research thrusts of: cause and prevention research; detection and diagnosis research; treatment research; and cancer biology. The control objectives are organized into major intervention areas of: prevention; detection, diagnosis and pretreatment evaluation; and treatment, rehabilitation and continuing care. The research and control components are complemented by support components consisting of cancer centers support, research manpower development and construction.

Cause and Prevention Research

Among the programs of cause and prevention research, the NCI is vigorously pursuing: (a) environmental carcinogenesis research to identify cancer-causing chemicals in the environment, including industrial chemicals, pesticides, food additives and drugs; (b) virus studies to further determine the role of viruses as causes of cancer in man; (c) demographic studies of the variations in cancer occurrence in geographic regions and among various age groups and races; (d) diet and nutrition projects which are designed to identify factors which may affect the risk of cancer; and (e) a smoking and health program which is involved in tobacco research, defining cigarette characteristics and identifying high-risk smokers and the development of drugs that may be helpful in smoking cessation.

Detection and Diagnosis Research

This research is carried out through programs in epidemiology, immunodiagnosis, diagnosis, and organ site task forces. One of the goals of cancer epidemiology is the identification of high-risk groups; the Cancer Surveillance Epidemiology and End Results Reporting (SEER) Program is one means of accomplishing this goal. Immunodiagnosis is concerned with the development of immunologic tests that indicate the presence of specific types of cancer. Several new types of equipment are in developmental stages for use in the screening and diagnosis of cancer. The automation of the reading of cancer cytology specimens through the use of machines will reduce the use of manpower required for such readings, but more important, it will increase the number that can be read in a given period of time. Success in the use of the scanner in the diagnosis of brain tumors has led to the expansion of efforts to develop similar scanners for localization of tumors elsewhere in the body. Task force efforts are presently concentrated in the commonly occurring cancers of the breast, lung, bowel, bladder, prostate, and pancreas.

Treatment Research

Twenty years ago, systemic treatment (drugs for cancer) was developed following the realization that cancer is most often a systemic disease. Even patients curable by local forms of treatment such as surgery or radiation have been shown to shed cancer cells into the blood stream. Over half of all patients who develop one of the many types of cancer die of it each year, even though it may appear to be localized. The success of testing various therapies in patients with advanced cancer has led to further testing in patients with apparently localized disease but with a high risk of recurrence of cancer. Thus, with each report of individual success in advanced cancer, it becomes more possible to mobilize the private medical community and the patient resources necessary to apply the investment in therapeutic research.

Cancer Biology

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. Cancer biology is essential to each of the other cancer program thrusts and constitutes the basic research nucleus which is critical to the implementation of the National Cancer Program.

Resource Development

Development of the network of cancer centers is based on the premise that the medical school, the specialized cancer institutions, and the practicing physician will all participate in an integrated endeavor to achieve the most effective cancer treatment and research effort. The primary purpose of the centers program is to achieve a demographic distribution of centers for conducting basic cancer research, promoting multidisciplinary approaches to the clinical management of cancer patients, demonstrating advanced techniques for cancer treatment, and at the same time serve as a national resource for training and community outreach efforts through the Cancer Control Program.

The training and education activities of the Institute are mainly supported by the National Research Service Awards Program and the Clinical Cancer Education Program. The National Research Service Awards Program supports fundamental research training in fields identified by the NCI as areas of crucial manpower needs. Eight general areas constitute the National Cancer Institute's research training emphasis: carcinogenesis, tumor biology, drug development, chemotherapy, viral oncology, immunology, radiation oncology, and epidemiology.

The Clinical Cancer Education Program, initiated in FY 1975, supports the improvement and expansion of cancer education at the undergraduate and graduate levels and promotes the continuing cancer education of physicians, dentists, and other health professionals in schools of medicine, dentistry, osteopathy, public health, in major hospitals affiliated with medical schools, and in specialized cancer institutions. Clinical Cancer Education grants support coordinated and innovative approaches to improving cancer teaching throughout the medical curriculum of recipient institutions.

Technological improvements and new research opportunities often necessitate the renovation of old and construction of new facilities so that the best and quickest advantage can be taken of such developments for research and direct benefit to people. A high priority need also exists for biohazard construction in order to provide safety to communities and to investigators working with chemicals and viruses which could be capable of causing cancer.

Cancer Control

Cancer Control funds are used as "seed" money, limited to prototype studies and not general health care delivery. All projects are expected to ensure a means of self-support following completion of the grant/contract period. The Cancer Control and Rehabilitation Advisory Sub-Committee on Reimbursement is developing guidelines to assist grantees and contractors to achieve self-support. Methods are being investigated to provide transition of control programs from field testing and demonstration into traditional support by third party payers.

Support Activities

In addition to the Research, Resource Development, and Cancer Control Programs of the National Cancer Institute, there are other activities which are complementary to those programs, including international activities, dissemination of cancer information, and interagency coordination.

The objectives of NCI efforts in international activities are to coordinate international cancer research and cancer control activities, and to further implement the International Cancer Research Data Bank program which provides the results of research to approximately 10,000 cancer researchers throughout the world. Important segments of the international program are carried out through the World Health Organization (WHO), International Agency for Research on Cancer (IARC), and the International Union Against Cancer (UICC). Bilateral agreements have been signed between the U.S. and the USSR; also with the governments of Japan and Poland. Proposed agreements are currently being developed with the governments of France and West Germany. Discussions of collaborative research activities are currently being held with other countries, including the Arab Republic of Egypt and the People's Republic of China.

Within the framework of the National Cancer Program, NCI continues to strengthen existing informational exchanges and develop new means to assure the dissemination of cancer information. This involves the active participation and coordination of governmental, private and voluntary groups, and organizations. In the communication of research information to physicians, NCI conducts a variety of activities. Conferences are held to help health professionals update their knowledge of advances in cancer. The communication activities of the centers, programs of cooperative clinical research groups, and organ-site programs provide other important avenues for channeling research information to physicians and other health professionals.

The NCI is continuing to broaden and formalize interagency coordination with other Federal organizations involved in cancer, cancer-related, and other categorical and noncategorical health activities. The two most recent efforts were the establishment of the Interagency Coordinating Committee for the National Cancer Program and the Interagency Coordinating Committee for Cancer Control and Rehabilitation.

The narrative justification and the Program Purpose and Accomplishment statements provide additional insight into these programs.

Research

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Cause and Prevention Research.....	581	$180,147,000	607	$199,537,000	581	$181,572,000	-26	-$17,965,000
Detection and Diagnosis Research.....	217	43,649,000	226	48,099,000	217	44,390,000	-9	-3,709,000
Treatment Research.....	599	217,093,000	624	240,735,000	599	221,229,000	-25	-19,506,000
Cancer Biology.....	375	112,168,000	390	124,270,000	375	116,071,000	-15	-8,199,000
Total Research.....	1,772	553,057,000	1,847	612,641,000	1,772	563,262,000	-75	-49,379,000
Budget Mechanism:								
Research Grants:								
Regular.....		128,367,000		157,731,000		134,395,000		-23,336,000
Non-competing.....		(101,351,000)		(101,351,000)		(112,844,000)		(+11,493,000)
Competing.....		(27,016,000)		(56,380,000)		(21,551,000)		(-34,829,000)
Specials.....		105,012,000		111,310,000		109,591,000		-1,719,000
Cancer Research Centers.....		(85,173,000)		(88,943,000)		(86,824,000)		(-2,119,000)
Other Specials.....		(19,839,000)		(22,367,000)		(22,767,000)		(+400,000)
Research and Development Contracts		191,314,000		213,173,000		181,384,000		-31,789,000
Intramural Research and Direct Operations:								
Laboratory and Clinical Research.....	437	21,174,000	455	21,477,000	437	23,544,000	-18	+2,067,000
Collaborative Research and Support.....	984	51,105,000	1,028	52,128,000	984	55,020,000	-44	+2,892,000
Research Management and Program Services.....	292	50,509,000	302	50,946,000	292	52,483,000	-10	+1,537,000
Program Management.....	59	5,576,000	62	5,876,000	59	6,845,000	-3	+969,000
Total.....	1,772	553,057,000	1,847	612,641,000	1,772	563,262,000	-75	-49,379,000

Cause and Prevention Research

Program Purpose

Cancer cause and prevention research is a program of laboratory, field and demographic research on the cause and natural history of cancer and means for preventing cancer. Through the program, evaluations are made of environmental carcinogenic hazards and mechanisms of cancer induction by viruses. This program serves as the focal point for the Federal government on the synthesis of clinical, epidemiological, and experimental data relating to the causes of cancer and for development of measures to prevent cancer in man.

The major programs of cause and prevention research include:

1) In the environmental carcinogenesis research area, the NCI supports a vigorous research effort to identify cancer-causing chemicals in the environment. These include industrial chemicals, pesticides, food additives and drugs. Tests are underway at 20 laboratories throughout the United States, including the Frederick Cancer Research Center. Under development is a new method for the rapid and less expensive testing of chemicals with potential cancer-causing activity.

2) In virus research scientists have carefully documented that viruses (both DNA and RNA) cause cancers in animals. Studies are being conducted to determine the role, if any, of viruses in the causation of cancer in man.

3) Within demographic research studies, the SEER (Surveillance, Epidemiology and End Results Reporting) Program has been initiated to monitor trends in cancer incidence, changes in diagnostic and treatment priorities and survival rates of cancer patients. This program studies the variations in cancer occurrence in geographic regions and with respect to age, sex, race and other demographic variables.

4) A Diet, Nutrition and Cancer Program has been established. Diet and nutrition projects are designed to identify groups of individuals or members of certain groups who may be at excess risk to cancer, thus providing clues to the identity of risk factors, such as food components, additives, contaminants and natural products.

5) The Smoking and Health Program is involved in tobacco research defining cigarette characteristics such as the types of tobacco, types of filters, quality of paper, and contribution of nicotine and tars to toxicity, which can be modified to produce less hazardous cigarettes. The program includes efforts to identify high-risk smokers and development of drugs that may be helpful in smoke cessation.

Program Plans

The 1977 budget estimate for cause and prevention research of $181,572,000 and 581 positions represents a decrease of $17,965,000 and 26 positions below the 1976 estimate. The program plans, along with expected accomplishments, are as follows:

Environmental Carcinogenesis Research

The continued expansion and increasing visibility of the Institute's role in environmental carcinogenesis will require additional documentation relative to the evaluation of carcinogenic risk from environmental exposures. Research efforts to identify cancer-causing chemicals in the environment will continue with approximately 450 chemicals under test. More detailed pathology evaluations and more stringent requirements for monitoring and data collection will be employed.

Cooperative efforts in coordination of environmental carcinogenesis activities with other Federal agencies will continue through joint problem-solving and cost-sharing projects. The Interagency Collaborative Group on Environmental Carcinogenesis, which has membership representing over 20 Federal agencies and subagencies, provides a mechanism for the exchange of technical information and attempts to identify action items which might be appropriate for inclusion under the National Cancer Program. Joint efforts in occupational carcinogenesis will continue to be pursued with the National Institute for Occupational Safety and Health. Cooperative efforts will continue with the regulatory and enforcement agencies including the Food and Drug Administration, Environmental Protection Agency, and Consumer Product Safety Commission.

Efforts to develop and validate new methodologies (in vitro) for the rapid and less expensive testing of chemicals with potential cancer-causing activity will be emphasized. This method will allow the Institute to determine the carcinogenic potential of a greater number of suspected chemicals in a much shorter time period. Activities to assist investigators in prevention of exposure to chemical carcinogens in the laboratory will be expanded.

Research will continue in the fields of lung, pancreatic, endocrine, digestive tract, and childhood cancers with emphasis on studying the pathogenesis of cancers having major impact but for which no good experimental model systems are available. Additionally, in the lung cancer area special studies continue in the response of respiratory tissues to carcinogenic exposures. The identification of host factors affecting susceptibility to carcinogens and of factors capable of inhibiting the carcinogenic process is being investigated in these systems.

Studies of carcinogen chemistry, metabolism, and toxicity will continue. Analytical methodology for detecting and measuring carcinogen levels in complex environmental systems and human tissues will be developed. Nitrosamine research continues to represent a high priority. Studies concerning the mechanism of carcinogenesis at the molecular, cellular and immunological level offer potential for the development of methods to inhibit the induction of cancer.

Radioimmunoassays, developed for several carcinogens and related compounds, will be studied. Radioimmunoassays can detect minute traces of cancer-causing chemicals in body fluids or foodstuffs and offer a potential for defining levels of exposure in population groups.

Support will continue for extending the services of a chemical repository which provides for the acquisition, synthesis, storage, and distribution of well-characterized reference materials to collaborative projects. Providing the services of such a repository to the entire cancer research community will help to maximize the scientific community's research into environmental carcinogenesis.

Virus Research

Research will continue in the interaction between viruses and environmental chemicals. Many environmental chemicals activate latent RNA tumor viruses in animal cells. These viruses are capable of transforming cells to malignancy. A more comprehensive study of this interaction will be undertaken to give a better insight into the role played by viruses in chemical carcinogenesis.

Molecular studies of the mechanisms of the interaction of viruses and cells will continue to be emphasized. The main target of these investigations is the nature of the reaction that turns a normal cell into a cancer cell. Studies are being conducted to determine the immunologic characteristics of

viruses. The results of these studies may ultimately be the basis for simple but powerful diagnostic or prognostic tests in man.

A major vaccine effort is aimed at treating or preventing cancer. Previous studies have shown that animals can mount an immune response to cancer virus proteins, especially those found on the surface of tumor cells. Experiments are underway to determine whether viral vaccines can stimulate these natural defense mechanisms sufficiently to protect the animal from cancer. In addition, research aimed at finding new viruses in humans or closely related species will continue to be supported.

Emphasis will be placed on the study of cellular control mechanisms that regulate viral expression. Although cancer virus expression appears to be largely repressed, there is some evidence that human tumor cells and indeed normal cells contain viral material that may be involved in the initiation of malignant growth. The best examples are found in breast cancer and acute myelogenous leukemia. In animal studies many factors have been identified that affect virus activity, among these are host genes, host immunologic responses and environmental stresses such as chemicals. Eventually these studies may enable us to find viruses in man and devise rational means for the prevention and treatment of human cancer.

Demographic Research Studies

The SEER Program will be studying the variations in cancer occurrence in geographic regions and among various age groups and races, and will provide cancer statistics on an annual basis. Lines of inquiry will be developed into environmental and occupational carcinogenesis utilizing data gathered from the Third National Cancer Survey (TNCS) and the SEER system. Etiologic studies will be started on special high risk sub-groups of the population. Mathematical models will be developed to describe cancer causes and treatment effects.

The national cancer mortality data by county will continue to be analyzed in order to identify high risk counties and groups of people, and to generate new hypotheses on the causes of cancer. Analytical field studies of specific population sub-groups will be designed and conducted in collaboration with local health departments and individual cancer research workers. These investigations will involve detailed exposure histories of high risk populations and comparison groups. The exposure categories with which these and other analytic studies will be concerned include radiation, occupation, general environmental pollutants, immunosuppression and therapeutic drugs and viruses, in an attempt to identify environmental determinants of cancer and important host-environment interactions. Expanded studies on host factors themselves will include continued etiological studies of childhood cancer and clinical-pathologic investigations of factors responsible for cancer in those families prone to cancer.

Diet, Nutrition and Cancer Program

This program is developing activities concerned with: (a) epidemiological studies in the U.S. designed to uncover dietary and nutritional determinants of cancer; (b) defining the characteristic of a "normal" diet and nutrient requirements in man; (c) studying molecular nutrition in normal and cancerous individuals and animals; and (d) studying carcinogenic consequences of an altered diet and nutrition such as dietary excesses, dietary deficiencies and hormonal and immunological imbalances. Planning sessions with top scientists in nutrition and related fields have been held. A project is currently being implemented for the overall coordination of the nutrition program.

Smoking and Health Program

The Smoking and Health Program has completed the development and evaluation of inhalation smoking machines for bioassay of smoke in small rodents and the beagle dog. Projects are now underway in both assay systems to evaluate less hazardous cigarettes based upon results from previous experiments using the mouse skin bioassay.

Detection and Diagnosis Research

Program Purpose

The goal of research in cancer detection and diagnosis is to develop better ways of finding cancer at an early stage, when treatment methods have a better chance of success. It is believed that improvements can be made in methods of early diagnosis, which can improve survival from cancer well before the development of fully effective treatment or prevention.

Activities in detection and diagnosis research include: (a) the identification of population groups at high risk to cancer; (b) the identification of conditions associated with cancer; (c) the development of procedures for screening population groups for cancer; (d) the prediction of individuals who will get cancer; (e) the confirmation of the presence of cancer in a single individual, and assessment of its exact location, extent and type; and (f) the attempt to predict the course of cancer in the individual patient as a guide to treatment, that is, how the characteristics of the specific cancer and individual patient govern the choice, degree and urgency of treatment.

Program Plans

The 1977 budget estimate for detection and diagnosis research of $44,390,000 and 217 positions represents a decrease of $3,709,000 and 9 positions below the 1976 estimate. The program plans, along with expected accomplishments, are as follows:

Epidemiology

The registries that support the SEER Program will be expanded with emphasis on increasing coverage of minority groups and developing more meaningful ways to capture diagnostically important information in the program. Variations in cancer incidence will be correlated with ethnic, geographic and industrial considerations to hasten the identification of both hereditary and environmental factors in cancer causation that may assist in identifying high risk populations. If such groups can be defined more precisely, screening for cancer will be more efficient and rewarding. The detailed county-by-county survey of cancer incidence, recently published, is a major accomplishment toward this goal. Another important element now receiving careful attention is the determination of the optimal frequency of screening both for finding cancer cases, and coupled with present treatment, for survival from cancer.

Immunodiagnosis

Immunodiagnosis is concerned with the development of immunologic tests that will indicate the presence of specific types of cancer. The area of immunodiagnosis is especially promising because of the extreme sensitivity and specificity of immunological reactions; but the approach to the goal of specific blood or skin tests for different types of cancer is a complex process. All cells have on their surfaces molecular groupings, or antigens, which seem to be unique to an individual. The surface antigens of cancer cells are different, and call forth reactions by the patient's immune system. These reactions may be the formation of neutralizing proteins or antibodies, circulating in the blood, or the sensitization of certain white blood cells also to neutralize the cancer cell antigens. Although these reactions are not strong enough to destroy the tumor in a patient with growing cancer, it should be possible to test for antibodies in blood specimens or in the skin, or to test for the tumor antigens themselves when shed into the blood, to prove the presence of cancer. The basic step in developing such tests is to isolate the tumor antigen. With the antigen one can test for reactivity to it in a patient, and can produce antibodies in an animal that can be used to test for the antigen itself in a patient's blood.

Encouraging progress has been made in the purification of the carcinoembryonic antigen (CEA) associated with cancer of the large bowel. This partly purified antigen promises greatly improved specificity in this immunodiagnostic test for bowel cancer. Another promising finding in cancer immunodiagnosis is that the number of thymus-derived lymphocytes, one type of white blood cells, is reduced when cancer is present in a patient. These and other findings will be followed up in detail to verify their accuracy for cancer diagnosis. Emphasis to date has been on cancer of the bowel, breast and lung. Work will be undertaken on ovarian cancer, in which clinical findings suggest that immunodiagnosis may be especially important.

Diagnosis

New equipment for use in both cancer screening and diagnosis is under development. Several avenues toward automation of the reading of cancer cytology specimens show promise but further development must take place before they can be used in mass screening. When perfected, these machines should save a great deal of manpower in the reading of cytology smears. The great success of computer-assisted tomography in the diagnosis of brain tumors has led to rapid expansion in efforts to develop similar scanners for the localization of tumors elsewhere in the body. These scanners rotate a tiny x-ray beam through the body, and by computer analysis of the transmission of these x-rays, reconstruct a cross-section of the body on a television screen. Development will be completed of prototype machines for ultrasonic mammography, a promising method for breast cancer screening without the use of x-rays. The use of similar ultrasonic devices will be explored for the diagnosis of liver and pancreatic cancer. Research will continue to work out standardized methods for evaluation of the quality of all imaging techniques, x-rays, ultrasound, and thermography so that objective judgments can be made of benefits and drawbacks of all these new techniques for imaging the body's internal organs for cancer diagnosis.

Task Forces

Certain efforts in detection and diagnosis of the common cancers of the breast, lung, bowel, bladder, prostate, and pancreas are supported by the various task force programs. In the Lung Cancer Program, a major clinical project in lung cancer screening will be continued to see if early case finding does, in fact, improve survival in the high-risk group of male cigarette smokers who are 45 years and older. Close to 50,000 such men are being screened at regular intervals by chest x-ray and sputum cytology. The project has already shown that early lung cancer can be detected in this way, and that the flexible fiberoptic bronchoscope can diagnose the exact location and extent for surgical treatment. It is expected that these patients will have much better rates of cure and length of survival than the usual cases of lung cancer. New cases will have to be added and followed carefully before this complex method of screening can be recommended for inclusion in the general practice of medicine. Through the Breast Cancer Task Force Program, a protein (estrogen receptor protein) is now under clinical trial for prognosis in advanced breast cancer. If the protein is present in the tumor, the cancer will respond to removal of hormone sources (ovaries, adrenals or pituitary); if not present, the patient can be spared a useless operation. In the Bowel and Prostate Task Force Programs, further developmental work is planned in biochemical and hormonal markers in blood, urine, and other fluids. Development of a simple test for occult blood in human feces will be investigated as a method of mass screening for early colo-rectal cancer.

Treatment Research

Program Purpose

The goal of the National Cancer Program in treatment research is to develop the means to cure as many patients as possible and to maintain control of the cancerous process. To achieve this goal, preclinical research is conducted to include the acquisition of materials and screening for antitumor agents, pharmacology and toxicology tests in animals, preclinical combined modality research, and the production and formulation of agents for clinical trials. Clinical trials research is conducted utilizing the modalities of chemotherapy, radiation therapy, surgery and immunotherapy. Cancer is most often a systemic disease, even patients curable by local forms of treatments such as surgery or radiation have been shown to shed cancer cells into the blood stream. Over half of all patients who develop one of the many types of cancer die of it each year, even though in many cases it may appear 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 widespread 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. Various therapies have been tested in those patients with far advanced cancer. The success in some patients has led to further testing in 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 success in advanced cancer, it becomes more and more possible to mobilize the private medical community and the patient resources necessary to apply the investment in therapeutic research.

Program Plans

The 1977 budget estimate for treatment research of $221,229,000 and 599 positions represents a decrease of $19,506,000 and 25 positions below the 1976 estimate. The program plans, along with expected accomplishments, are as follows:

Preclinical Research

The screen for antitumor agents will be modified to validate and broaden animal tumor systems so as to predict more accurately the anticancer effect of drugs or immunotherapy in humans.

Treatment-related research conducted in viral oncology includes studies of combined chemoimmunotherapy of virus-induced malignancies. Substances will continue to be tested for their ability to interfere with the biochemical pathways of viral replication and cell transformation and to enhance the host-immune response.

Clinical Research

Two major studies have shown that chemotherapy after mastectomy significantly lowers the recurrence rate in women with breast cancer whose lymph nodes show evidence of tumor. Studies will be pursued to maintain the same research level in order to define these exciting results through the use of new regimens and the addition of immunotherapy. The ultimate goal is to increase survival while reducing the extent of mutilating surgery required to control the tumor. Support will continue to the current trials of post-operative therapy with L-PAM, CMF (a drug combination) and immunotherapy in patients with positive lymph nodes.

Gastrointestinal adenocarcinomas count for one-fourth of all cancer deaths in the United States. In large bowel and stomach cancer new active chemotherapy regimens have been developed for the treatment of advanced stages of this disease. The use of these regimens immediately after surgery to increase the cure rates with the primary treatment is now underway. If successful, these studies could impact on 49,000 persons per year that ultimately die of colon cancer. Modest support will be provided to continue clinical trials of adjuvant chemotherapy with drugs and immunotherapy with MER-BCG, a newly developed drug combination.

For other clinical trials, similar activities will be continued at the same level in all the major tumor types where traditional therapy (surgical removal of visible tumor) fails to cure a meaningful number of patients. In addition, new leads have emerged in ovarian cancer, the fifth most common cancer killer of women. Emphasis will be placed on this cancer, where chemotherapy can be successful in patients with advanced ovarian cancer. 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.

Phase II (to study chemotherapy--single agents or combinations--or combined modality regimens for initial efficacy evaluation) and Phase III (to study chemotherapy or combined modality regimens having highest priority for efficacy, evaluation in a controlled clinical setting) trials of drugs and new types of immunotherapy in various common cancers will be continued at cancer centers throughout the country.

The Clinical Cooperative Group Program which consists of 23 groups and represents one of the principal programs conducting clinical trials will be maintained. Funds will be directed towards the establishment of surgical oncology, radiation oncology and pathology within each group to begin to further develop a complete combined modality potential.

Collaborative arrangements for clinical trials of new drugs, immunotherapy, combined modalities, high LET radiation, and new schemes of radiation time/dose/volume fractionation will continue to be pursued. Methods of applying heat as an adjuvant to cancer treatment with drugs in humans have been developed and will be implemented in clinical trials.

Efforts to determine and test for biological markers--substances found in the blood or urine correlating with the presence of tumor--will be continued and the results will be integrated with clinical trials currently in process.

The SEER Program will continue to cooperate with the World Health Organization in field testing and oncology coding systems, specifically, assistance in the ninth revision of the International Classification of Disease (Oncology). This system will be used by tumor registries throughout the world in order to uniformly code the type and primary site of cancer.

Cancer Biology

Program Purpose

Cancer biology relates to all programs of the National Cancer Plan. Knowledge of the fundamental molecular and cellular changes accompanying the initiation of division, growth, regulation, and development of normal cells and abnormal growth of malignant cells is essential for an understanding of the cause of cancer and provides a basis for attacking problems of diagnosis, treatment, and prevention of cancer. Cancer biology encompasses two major areas of concern. The first is the transformation of normal cells into cells characterized by a potential for uncontrolled growth. This involves alteration of cellular chemistry by a spectrum of cancer-causing agents, including chemical carcinogens, oncogenic viruses, radiation acting alone or in combination with genetic, nutritional and perhaps other factors. The second concern is the metastatic spread of the malignant cells to other sites. This spread is accompanied by alterations in structure or function of cells, which allows them to escape the body's usual defenses.

Most of the basic biological disciplines are involved in the understanding of these processes. Pathology, cell biology and kinetics, molecular biology, genetics, physiology, ultrastructural analysis, morphogenesis, developmental biology, immunology and other related disciplines are all concerned with cancer biology. Cancer biology is thus basic to each of the cancer program thrusts and constitutes the research base essential to the implementation and progress of the National Cancer Program.

Program Plans

The 1977 budget estimate for cancer biology of $116,071,000 and 375 positions represents a decrease of $8,199,000 and 15 positions below the 1976 estimate. The program plans, along with expected accomplishments, are as follows:

Research will continue on studies aimed at understanding the structure and function of normal cells down to the molecular level as well as studies into what changes occur when the cell becomes cancerous. Investigations will continue to further the understanding of how and why cancers spread, including a study of factors promoting or arresting the metastases. According to an important theory, metastatic potential is determined by the surface properties of tumor cells. The problems of cell membrane biology are complex and must be approached from various disciplines. To understand the role of the cell surface membrane in the regulation of abnormal growth, studies will seek detailed knowledge of the biological, physical, and chemical properties of the membrane and of its organization and dynamics.

Explorations of mechanisms by which tumor cells escape destruction by the immune system will be conducted. There is a need for further development of animal model systems for the application of recently developed immunological techniques.

Indications that there are genetic and nutritional influences on cancer susceptibility and induction will be investigated. There is evidence that only a small part of cancer virus genetic material directs or controls tumor induction. This information indicates an opportunity to separate the cancer gene from other virus genes. Isolation of the viral cancer gene would simplify efforts to understand the transformation of normal cells into tumor cells. Basic research will be continued into nutritional factors affecting the molecular structure in normal and cancerous individuals and animals.

The Frederick Cancer Research Center will continue to serve a vital role in producing a variety of resources including cell lines, sera, viruses and laboratory animals. The basic research program on the immunobiology of cancer will be continued as well as research on biological markers.

Resource Development

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Cancer Centers Support	14	$31,915,000	15	$34,435,000	14	$32,310,000	-1	-$2,125,000
Research Manpower Development	15	27,466,000	16	31,323,000	15	27,758,000	-1	-3,565,000
Construction	12	22,577,000	13	25,577,000	12	10,907,000	-1	-14,670,000
Total	41	81,958,000	44	91,335,000	41	70,975,000	-3	-20,360,000
Budget Mechanism:								
Research Grants:								
Specials		39,074,000		45,401,000		39,325,000		-6,076,000
Fellowships		12,840,000		12,840,000		16,399,000		+3,559,000
Training Grants		5,323,000		5,323,000		1,764,000		-3,559,000
Intramural Research and Direct Operations:								
Research Management and Program Services	38	2,539,000	41	2,589,000	38	2,923,000	-3	+334,000
Program Management	3	182,000	3	182,000	3	225,000	---	+43,000
Construction:								
Grants		17,000,000		20,000,000		7,339,000		-12,661,000
Contracts		5,000,000		5,000,000		3,000,000		-2,000,000
Total	41	81,958,000	44	91,335,000	41	70,975,000	-3	-20,360,000

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Cancer Centers Support

Program Purpose

The cancer centers support activity of the National Cancer Institute provides funds for developing centers which will generate new knowledge of cancer and which will accelerate the transfer of knowledge of improved cancer prevention, treatment, and rehabilitation to health professionals and the general public in their surrounding communities.

This activity is carried out by the award of Cancer Centers Support Grants (Core Grants and Exploratory Studies Grants) for: (1) enhancing institutional coordination of cancer projects; (2) providing program stability and development at centers; (3) improving multidisciplinary approaches to cancer research, training, treatment and demonstration; and (4) assisting in the development of community affiliations that expedite education and outreach projects.

Program Plans

The 1977 budget estimate for cancer centers support of $32,310,000 and 14 positions represents a decrease of $2,125,000 and 1 position below the 1976 estimate. The program plans, along with expected accomplishments, are as follows:

The centers play a vital role in the NCI's National Cancer Program by providing the cancer expertise and specialized facilities necessary for coordinating many efforts supported by various sources including NCI, American Cancer Society, state and local governments, university resources and private philanthropy.

The National Cancer Institute has recognized that 17 centers have met or are rapidly meeting the criteria for Comprehensive Cancer Centers set down by the National Cancer Advisory Board. The criteria emphasize an environment of excellence in both basic and clinical science that assures high quality research, outstanding interdisciplinary clinical capabilities, an organized cancer detection program, a statistical base for research support and for internal evaluation, an effective community outreach program, multidisciplinary research training and an organization that provides stability and coordination.

New endeavors in comprehensive centers link the efforts of the NCI centers program with other NCI programs. These new endeavors include a minimal patient data system as part of the International Cancer Research Data Bank and a network of Centers Communications Offices associated with the NCI Communications Office and Division of Cancer Control and Rehabilitation.

The Cancer Centers Program in cooperation with the Cancer Control Program enhances community outreach efforts which transmit recent treatment research findings to professional and lay people who may not have direct affiliation with a cancer center. Physicians located in community hospitals in areas surrounding Comprehensive Cancer Centers may easily consult with the Centers' investigators. Programs being developed and currently underway make experimental results, acquired research and treatment findings available to professional and lay people who may not have direct affiliation with a cancer center.

Physicians located in community hospitals in areas surrounding cancer centers may easily consult with and relate to the center investigators who are in their specialty areas. Programs presently being developed and some currently underway are targeted to make the knowledge acquired by investigators in comprehensive centers more readily available to both the professional and lay public.

FY 1977 will witness the continuing gradual emergence of a network of geographically strategic, programmatically balanced, and nationally coordinated centers. Although some will be mature and others will be relatively new, they will provide a national base for the continued implementation and evaluation of a wide variety of NCI efforts in the attack upon cancer. Community outreach activities, as the newest element of this total endeavor, should be more fully established, and contribute substantially to the tangible impact of the centers upon their surrounding populations through increased availability of consultation, professional education, and public information assistance.

Cancer centers, both comprehensive and specialized, will continue to be an integral resource for research conducted through the National Cancer Program. Research will continue to be pursued in the research thrust areas of cause and prevention research, detection and diagnosis research, treatment research and cancer biology.

Research Manpower Development

Program Purpose

Research manpower needs in specific disciplines which are important for fulfilling the National Cancer Program are met by providing fellowships, training grants, and education awards. The programs include the National Research Service Awards Program, the Clinical Cancer Education Program, the Research Career Development Award Program and the Research Career Award Program.

The National Research Service Awards Program supports research training in eight areas: carcinogenesis, tumor biology, drug development, chemotherapy, viral oncology, immunology, radiation oncology and epidemiology. The Clinical Cancer Education Program supports the improvement and expansion of cancer teaching at the undergraduate and graduate levels in schools of medicine, dentistry, osteopathy, public health, in major hospitals affiliated with medical schools and in specialized cancer institutions. The program also promotes the continuing cancer education of physicians, dentists and other health professionals. The Research Career Development Award Program provides support for young scientists who show potential for developing into outstanding independent investigators in the cancer-related sciences. The Research Career Award Program, which is being phased out, provides lifetime stipends to accomplished cancer research specialists.

The Graduate and Clinical Training Program and the Research Training Program are being phased out and replaced by the National Research Service Awards Program.

Program Plans

The 1977 budget estimate for research manpower development of $27,758,000 and 15 positions represents a decrease of $3,565,000 and 1 position below the 1976 estimate. The program plans will allow the awarding of approximately 305 individual and 78 institutional awards under the National Research Service Awards Program. These awards will continue to support training in the fundamental disciplines of cancer research: biology, molecular biology, biochemistry, pharmacology, hematology, embryology, pathology, physics, genetics, medical oncology, epidemiology, chemotherapy, and surgical oncology. Training in these disciplines will provide investigators for the eight major cancer research areas.

Carcinogenesis, the first major research area, is concerned with mechanisms whereby certain environmental chemicals cause cancer. New methods must be developed to test the potential carcinogenicity of ever-increasing numbers of chemicals to which people are exposed. Moreover, innovative techniques are needed to detect cancer in people and in research animals in its earliest stages and to protect them against cancer induced by chemical carcinogens. The second major 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. Drug Development, the third major research area, involves the synthesis and evaluation of chemicals which are maximally effective against cancer and minimally toxic to patients. Chemotherapy research seeks to improve treatment with new as well as currently available chemicals. Expertise in this area requires knowledge of both basic and clinical pharmacology. Viral Oncology, the fifth major area, explores the role of viruses in the etiology of cancer. Studies are conducted at the cellular and molecular levels and include investigations of gene expression and cell regulatory functions. Immunology is an especially active field of cancer research which explores the failure of the immunological system as a possible cause of cancer. Immunotherapy investigations seek means of altering the immune response in an effort to cure or ameliorate cancer. Radiation Oncology, the seventh major area, encompasses both basic and clinical research, including studies of interactions between radiation

and other therapeutic agents. Other studies seek agents which alter cell kinetics to improve the use of radiation in treating cancer. Finally, Epidemiology provides mathematical and statistical approaches for assessing cancer etiology and for evaluating the efficacy of detection and treatment programs.

The Clinical Cancer Education Program will support approximately 51 institutional awards for coordinated and innovative cancer teaching in schools of medicine, dentistry, osteopathy, and public health, in major hospitals affiliated with medical schools, and in specialized cancer institutions.

Research Career Development Awards will support 115 individuals who show outstanding potential for developing into independent investigators of high quality in sciences related to cancer. Research Career Awards will continue to provide stipends to accomplished cancer research specialists. The support for all programs is summarized in the table below:

	(In thousands)			
	1975 Actual	1976 Est.	TQ Est.	1977 Est.
Research Manpower Development Program				
National Research Service Awards.....	$10,772	$11,285	$2,555	$16,184
Clinical Cancer Education Program....	5,033	8,492	---	5,000
Research Career Development Awards...	2,524	2,958	113	2,618
Research Career Awards.....	282	282	28	282
Graduate & Clinical Training Program.....	9,736	5,323	---	1,764
Research Training Program.....	2,596	1,555	---	215
Staff and Other Support.....	952	1,428	424	1,695
Total.....	$31,895	31,323	3,120	27,758

Construction

Program Purpose

Within the provisions of the National Cancer Act of 1971, as amended in 1974, the National Cancer Institute is authorized to support new construction, modernization and renovation of outdated research facilities and new construction for biohazard containment facilities. The construction and modernization of space for cancer research aids the development of comprehensive and specialized cancer research centers authorized under the National Cancer Act and also enhances existing centers and other research institutions. Construction funds are also used to modernize and renovate facilities on the NIH campus and at other Federal facilities including the Frederick Cancer Research Center. Support is provided for basic research laboratories, clinical research facilities, animal facilities, and biohazard facilities. Each construction project is approved and funded only after a thorough review of the research program for scientific merit, competence, and role in the National Cancer Program. Therefore, funds to improve cancer research space are committed only where there is a demonstrated need for modern and safe laboratories--safe with respect to proper containment of hazardous materials to protect the community and environment. Through construction grants, the National Cancer Institute provides up to 75 percent of eligible construction costs with at least 25 percent being provided by the grantee from non-Federal sources.

Program Plans

The 1977 budget estimate for construction of $10,907,000 and 12 positions represents a decrease of $14,670,000 and 1 position below the 1976 estimate. These 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, and other new construction in exceptional cases. The Department of Labor, Occupational Safety and Health Administration, 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 into the surrounding community. With the 1977 funds, additional renovation and modernization projects will also be accomplished on the NIH campus and at the Frederick Cancer Research Center. It is estimated that the funds can meet the alteration and renovation needs of five institutions for a total of 63,000 square feet in FY 1977. The 1977 funds will improve clinical research space and laboratories relating to virology, carcinogenesis, immunology, chemotherapy and radiation therapy. Construction of biohazard containment facilities will be supported at two institutions for a total of 10,000 square feet.

Funds in this budget exclude $8,661,000 which is now reflected in the NIH Buildings and Facilities budget request for support towards construction of the Ambulatory Care Research Facility at the NIH Clinical Center.

Cancer Control

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Cancer Control	74	$53,299,000	77	$58,671,000	74	$53,433,000	-3	-$5,238,000
Total	74	53,299,000	77	58,671,000	74	53,433,000	-3	-5,238,000
Budget Mechanism:								
Intramural Research and Direct Operations:								
Research Management and Program Services	21	1,577,000	22	1,592,000	21	1,702,000	-1	+110,000
Program Management	4	273,000	4	273,000	4	345,000	---	+72,000
Cancer Control:	49	51,449,000	51	56,806,000	49	51,386,000	-2	-5,420,000
In-house	(49)	(3,052,000)	(51)	(3,082,000)	(49)	(3,482,000)	(-2)	(+400,000)
Contracts		(42,262,000)		(46,589,000)		(38,904,000)		(-7,685,000)
Grants		(6,135,000)		(7,135,000)		(9,000,000)		(+1,865,000)
Total	74	53,299,000	77	58,671,000	74	53,433,000	-3	-5,238,000

Cancer Control

Program Purpose

The NCI Cancer Control Program is responsible for coordinating all cancer control activities in cooperation with State health departments and other health agencies. The Program is responsible for establishing programs that promote the transfer of existing information and new knowledge obtained through research activities to the lay public and practitioners of medicine and public health. The major objective of the Program is to identify, field test, evaluate, demonstrate, and promote widespread application of available and new methods that are effective in preventing the occurrence of cancer, minimizing its impact, and reducing the number of deaths. The Program's activities are grouped into three major intervention areas: (1) Prevention; (2) Detection, Diagnosis, and Pretreatment Evaluation; and (3) Treatment, Rehabilitation, and Continuing Care. Cancer Control deals primarily with subgroups of populations at risk to cancer providing methods and techniques which can be applied to the larger at-risk populations by the appropriate members of the health profession and the public.

By field testing and evaluating new methods and techniques of cancer control on a limited basis in a controlled setting, the Cancer Control Program is able to use its funds as "seed money", limiting demonstration and application activities to prototype studies, thus avoiding general health care delivery activities.

Program Plans

The 1977 budget estimate for cancer control of $53,433,000 and 74 positions represents a decrease of $5,238,000 and 3 positions below the 1976 estimate. The program plans, along with expected accomplishments, are as follows:

Prevention

The Cancer Control Program will continue to support the Tyler, Texas, and Louisville, Kentucky, projects which represent prototype cancer control prevention approaches for occupational exposure to proven carcinogenic substances. Through education programs the potential of these two studies will yield approaches which, if utilized by labor, industry and health professionals could impact on millions of asbestos and vinyl chloride workers.

Based on the results of the Survey of Exposure to Chemical Carcinogens, which is assessing and prioritizing currently known carcinogenic substances, comprehensive prevention strategies will be implemented in those industrial settings which have immediate cancer control potential.

Support will be continued for the Communication Network (Controline) which has been established through the 17 Comprehensive Cancer Centers, utilizing a toll-free telephone service in each Center's Communications Office. This system will give each individual in the U.S. access to what is known about cancer. Also, the network offices will decentralize the dissemination of cancer information to centers of excellence throughout the country.

A two-year industrial stewardship project will continue to provide an understanding of what is involved in the avoidance of potential carcinogens and in detection necessary after exposure. Education programs developed will be aimed at high/mid-level management. A second program, carried out in conjunction with the Occupational Safety and Health Administration, will develop programs for workers and new supervisors in the problems of occupational carcinogenesis.

Detection, Diagnosis, and Pretreatment Evaluation

Support will continue for the 27 Breast Cancer Detection Demonstration Projects, jointly sponsored by the Cancer Control Program and the American Cancer Society, involving 270,000 asymptomatic women with early screening by clinical history, clinical examination, mammography (xeroradiography) and thermography. To date 125,000 women have been examined, with 5,000 recommended for biopsy. 80% of confirmed cancers had no regional node involvement compared to 45-50% nonregional node involvement in a series which did not utilize early detection methods. In the current detection units, mammography is proving to be a valuable technique since 40% of the cancers are detected by mammography alone.

Projects to train practicing physicians in mammography and thermography techniques for the early detection of breast cancer will continue with the American College of Radiology. These projects are a natural progression following the success of the 27 Breast Cancer Detection Demonstration Projects.

Through 1977, at least 32 states will continue to participate in cancer control projects dealing with women at high risk to cervical cancer for the development of screening programs utilizing the Pap test. The population with risk factors of greatest importance in uterine cervix cancer and which is not regularly screened represents the population emphasized by the Cancer Control-State health department programs. By the end of 1977, an estimated 3.5 million screenings will have been performed. These studies will provide information on the frequency of screening, population to be included, the most effective settings and the nature of follow-up which should be required.

Six radiologic physics centers coordinated by the American Association of Physicists in Medicine will continue to be responsible for monitoring the dosimetry for therapeutic and diagnostic radiology in all cancer control projects. This important quality control mechanism can serve as a model for the benefit of the millions of Americans undergoing medical diagnostic radiologic procedures yearly and the more than 400,000 cancer patients receiving therapeutic radiation yearly.

Support will be continued for two projects to evaluate the efficacy of techniques for the diagnosis and localization of early lung cancer before it has progressed to the x-ray positive state.

Treatment, Rehabilitation, and Continuing Care

Three series of prototype demonstration networks, linking community hospitals to an experienced cancer hospital, have been organized for the following cancer sites: Breast Cancer (12 networks); Head and Neck Cancer (10 networks); and Childhood Leukemia and Lymphoma (7 networks). The impact of these networks which deal directly with 9,400 new cancer patients each year can be expected to provide the development of techniques for the diagnosis and application of new methods of treatment and rehabilitation for these specific cancer sites which have an annual incidence of 142,600 cases.

The Cancer Control Program will continue to support several projects that identify the resources, facilities and services needed in the outpatient clinic and at-home for the rehabilitation and/or continuing care of oncology patients, including the development and implementation of an at-home rehabilitation program. These projects are carried out in a variety of institutional settings (cancer centers, medical schools, community hospitals and at-home). Approximately 150,000 patients are expected to benefit over a three-year period directly and another 2.0 million patients could benefit indirectly.

The training of health professional groups necessary for cancer control is helping to complete the continuum of cancer control. These groups include an estimated 3,600 physical and occupational therapists, rehabilitation teams, maxillofacial prosthodontists, enterostomal therapists and nurse oncologists.

Continued support of several projects will be provided for modification of employers' attitude toward the employment of work-able cancer patients. A sampling of 1,000 employers and 750 cancer patients is in process to determine any bias toward hiring of cancer patients. If found, programs will be developed, tested and evaluated for positive employment action on the hiring of cancer patients.

Several behavioral studies will continue through 1977, including the support of several projects to develop a program to demonstrate the benefits of early identification of psychosocial problems and early intervention toward rehabilitation of cancer patients and projects that will analyze the psychological impact of breast cancer on potential and actual victims and their families.

Continued support will be given to projects for demonstrating proven and practical methods of cancer detection, diagnosis, pretreatment evaluation, treatment, rehabilitation and continuing care in the Community-Based Cancer Control Program. The Community-Based Cancer Control Program is especially intended to inform health professionals and the public about the effectiveness of these cancer control interventions. Programs that will be emphasized include acute childhood leukemia, Hodgkin's disease and non-Hodgkin's lymphoma, multidisciplinary teams in treatment decisions, and combined modality treatment.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
607	$199,537,000	$1,073,500,000[1/]	581	$181,572,000

Purpose: Cause and prevention research has four main objectives: (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 thrust is conducted in government laboratories and in academic and private institutions. Research in the academic and private sector is accomplished through the funding of 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, prostate and pancreas task forces are also identified within this research area.

Accomplishments in 1976: (1) In the carcinogenesis bioassay area a new structure for increased development and validation of a battery of cell culture methods for screening environmental chemicals has been established; (2) evidence has been found to show that viruses and chemicals can interact to cause cancer in animals; (3) a new avenue for exploitation was opened through studies of site-specific cancer deaths, 1950-1969, by county within the United States; (4) the development and evaluation of inhalation smoking machines for the bioassay of small rodents and the beagle dog were completed; (5) radioimmunoassays for the detection of minute traces of cancer causing chemicals in body fluids or foodstuffs have been developed; and (6) the association of herpesviruses, which have been found to cause cancer in primates, with tumors of the head and neck and urogenital tract have been demonstrated.

Objectives for 1977: Research efforts in this area will be continued to include: research in the search for other cancer viruses; further assessment of carcinogenic risk from environmental exposure; continued evaluation of less hazardous cigarettes; and studies to uncover dietary and nutritional determinants of cancer.

1/ For all programs of NCI including $88,500,000 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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
226	$48,099,000	$1,073,500,000[1/]	217	$44,390,000

Purpose: 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 goals of this research are three general areas of investigation: detection, diagnosis and prognosis. The goal of research in detection is to be able to identify those groups that are most susceptible to cancer within large populations of apparently healthy people. Research in diagnosis is concerned with improving the methods of determining the presence and precise location of cancer in the individual. Research in prognosis is aimed at improving the prediction of the growth, spread and response to treatment of the individual's cancer. Research in detection and diagnosis is carried out in government facilities and in academic and private institutions through the funding of research grants and research and support contracts.

Accomplishments in 1976: (1) Completion of the U.S. county-by-county survey of cancer mortality rate has provided a prospective identification of groups at high risk to cancer from environmental contaminants; (2) a prototype cell-sorting machine has been developed to screen cervical cytology specimens automatically at the rate of 15-25 per hour. This is a significant step toward the goal of automation of the reading of Papanicolaou smears; (3) the development of computer-assisted x-ray tomography has vastly improved the diagnosis of brain tumors in the clinic, easily showing the location and extent of tumors never before observable by x-ray; (4) the study of sputum cytology for detection of lung cancer in smokers without symptoms of the disease followed by fiberoptic bronchoscopy for tumor localization, has screened 20,000 individuals and found 154 cancers; and (5) a clinical test involving the estrogen receptor protein has been developed which indicates whether the tumor in a breast cancer patient will respond to removal of hormone sources (ovaries, adrenals, or pituitary). If the test indicates no response, the patient will have been spared a useless operation.

Objectives for 1977: Research efforts in this area will be continued to include: refinement of automated machines to assist in cervical cytologic screening for cancer; development of ultrasonic scanning for mammography to avoid all ionizing radiation; and investigation of newer immunologic reactions of importance in cancer.

1/ For all programs of NCI including $88,500,000 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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
624	$240,735,000	$1,073,500,000 1/	599	$221,229,000

Purpose: Included within this activity is the national program for research in the treatment of patients with cancer, whose goal is to "develop the means to cure as many patients as possible and to maintain control of the cancerous process". 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 facilities 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 underway to broaden the activities of the clinical cooperative groups to include combined modality treatments. Research treatment by the use of surgery, radiation, immunotherapy and chemotherapy either used singly or in combination is a major segment of current research efforts.

Accomplishments in 1976: (1) In breast cancer the use of a three drug regimen in the post-operative period has led to an even more dramatic drop in the recurrence rate than was observed in earlier studies using a single drug; (2) the first effective drug combination for the treatment of advanced colon cancer has emerged; (3) the two-year survival rate for patients with osteogenic sarcoma, a tumor of the bone in young people, has been increased from 20 to 80 percent through the use of combined modality treatment; (4) advances were made in the use of biological marker substances found in the blood or urine correlating with the presence of tumor to determine the extent of breast cancer; and (5) the addition of immunotherapy to chemotherapy in patients with acute myelogenous 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 1977: Research efforts in this area will be continued to include: studies in breast cancer research using chemotherapy after mastectomy; further emphasis on ovarian cancer, the fifth most common killer of women; and expanded surgical oncology, radiation oncology, and pathology within the Cooperative Group Program in order to begin to develop a more complete combined modality potential.

1/ For all programs of NCI including $88,500,000 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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
390	$124,270,000	$1,073,500,000 1/	375	$116,071,000

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: Research in cancer biology is concerned with why a normal, healthy cell becomes malignant and, after this change occurs, why the cell grows, multiplies and spreads to other areas of the body.

Accomplishments in 1976: (1) General differences between the membranes of normal and malignant cells have been demonstrated. Different growth characteristics of normal and transformed cells may be caused by primary membrane changes. These changes may affect the enzymes thus influencing the regulation of cell proliferation; (2) a substance extracted from the starfish has a damaging effect on cancer cells. Initial investigations are underway to identify and determine its potential as a treatment for cancer; (3) new evidence shows that only a small part of a cancer virus' genetic material directs or controls tumor growth. Isolation of that cancer gene from other genes of the virus would help in understanding the transformation of normal cells to cancer cells.

Objectives for 1977: Research efforts in this area will be continued to include: research into the mechanisms by which cancers spread. Information on those factors promoting or arresting the growth of metastases could lead to improved methods of control; continued efforts to learn more about the biological, chemical and physical properties of the cell surface membrane; and explorations into why tumor cells avoid normal body immune systems.

1/ For all programs of NCI including $88,500,000 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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
15	$34,435,000	$1,073,500,000 1/	14	$32,310,000

Purpose: The cancer centers support activity provides core grants and grants for exploratory projects in support of the Cancer Research Centers Program of the National Cancer Institute. Core grants provide support for the administration, common services and collaborative activities of cancer centers as well as "seed money" for development of new programs within the centers. Exploratory projects provide assistance to institutions planning multidisciplinary programs of research and treatment in cancer.

Explanation: 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.

Accomplishments in 1976: Currently the NCI has recognized 17 Comprehensive Cancer Centers. In 1976, 32 core grants will be supported. In addition, 32 exploratory projects will provide support in many areas of the country to determine the feasibility of establishing cancer centers.

Objectives for 1977: Core support for cancer centers will continue as in 1976 commensurate with development of the Cancer Research Centers Program. Approximately 13 exploratory projects will be supported.

1/ For all programs of NCI including $88,500,000 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)

1976 Estimate		1977	1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
16	$31,323,000	$1,073,500,000[1/]	15	$27,758,000

Purpose: The research manpower development program provides support for fellowships and training grants in various scientific fields related to cancer research. In addition, the Clinical Cancer Education Program 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 1976: During 1976, the Institute will award 957 fellowships and 46 graduate and clinical training grants in such disciplines as carcinogenesis, epidemiology, radiation, viral oncology, immunology, chemotherapy and tumor biology. In addition, 91 grants through the Clinical Cancer Education Program will be awarded to provide resources to schools of medicine, dentistry and osteopathy.

Objectives for 1977: It is estimated that the Clinical Cancer Education Program will provide resources for the awarding of 51 grants to medical, dental and osteopathic schools. Approximately 1,089 individuals will be supported through fellowship awards. Of the awards supported under the National Research Service Act, 25% will be committed to funding individual fellowships.

1/ For all programs of NCI including $88,500,000 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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
13	$25,577,000	$1,073,500,000[1/]	12	$10,907,000

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 1976: In 1976 $25,577,000 will support the upgrading and construction of cancer research facilities including various comprehensive and specialized cancer centers. These funds will permit the modernization and creation of additional cancer research space which is essential to the achievement of the research and cancer control goals of the National Cancer Program. Additional renovation and modernization projects will be supported on the NIH campus as well as at the Frederick Cancer Research Center.

Objectives for 1977: Funds requested for 1977 are $10,907,000. These funds will permit new construction, alteration and renovation of existing facilities and the completion of shell space and biohazard and containment laboratories for the continuation and development of the cancer program. The program provides facilities for expanding meritorious, balanced, and coordinated cancer research and control programs. The need for additional and updated facilities is a consequence of developing new research leads and new approaches to cancer care.

1/ For all programs of NCI including $88,500,000 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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
77	$58,671,000	$88,500,000 1/	74	$53,433,000

Purpose: As established in the National Cancer Act of 1971, the cancer control program has the responsibility of bridging the gap between research and application in the practice of medicine and public health in order 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 research and development and demonstration findings to the practitioners of medicine and public health, educate practitioners and laymen in the latest cancer research findings; and stimulate the general application of effective control measures.

Accomplishments in 1976: The cancer control program supported projects in many different areas of the cancer problem. Prototype studies for the education of employees and employers on industrial carcinogens are in progress in Tyler, Texas and Louisville, Kentucky. Three series of networks have been organized in breast cancer, head and neck cancer and childhood leukemia and lymphoma to develop diagnostic, treatment and rehabilitation techniques for specific cancer sites. A Communication Network (Controline) has been established through the 17 Comprehensive Cancer Centers allowing each individual in the U.S. access to what is known about cancer. At least 32 states are continuing to participate in the screening of women at high risk to cervical cancer utilizing the Pap test. Support is being continued to the 27 Breast Cancer Detection Projects jointly sponsored by the Cancer Control Program and the American Cancer Society to involve 270,000 asymptomatic women with early screening by clinical history, clinical examination, mammography and thermography.

Objectives for 1977: The cancer control program will continue to support ongoing projects in all of the intervention areas with emphasis on industrial carcinogens, breast cancer, cervical cancer and new treatment and rehabilitation techniques.

1/ This is included in total authorization of $1,073,500,000.

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Estimate	Transition Quarter
1. Research:		
a. Cause and prevention research	$199,537,000	$38,397,000
b. Detection and diagnosis research	48,099,000	12,168,000
c. Treatment research	240,735,000	50,610,000
d. Cancer biology	124,270,000	25,663,000
Subtotal	612,641,000	126,838,000
2. Resource development:		
a. Cancer centers support	34,435,000	5,791,000
b. Research manpower development	31,323,000	3,120,000
c. Construction	25,577,000	4,120,000
Subtotal	91,335,000	13,031,000
3. Cancer control	58,671,000	11,655,000
TOTAL	762,647,000	151,524,000
(Standard Level User Charge)	(943,000)	(280,000)

The research pursued by the National Cancer Institute consists of cause and prevention research, detection and diagnosis research, treatment research and cancer biology. These activities will be supported during the Transition Quarter at a level that will permit the continuance of 1976 activities through grants, contracts and in-house research.

Resource development efforts of cancer centers support, research manpower development and construction will be supported at a level that will allow the continuance of 1976 activities.

Cancer Control activities will also be supported at a level to permit the continuance of 1976 activities.

WEDNESDAY, FEBRUARY 25, 1976.

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES

WITNESSES

DR. G. DONALD WHEDON, DIRECTOR
DR. DONALD S. FREDRICKSON, 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
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. NATCHER [presiding]. The committee will come to order.

We take up at this time the National Institute of Arthritis, Metabolism, and Digestive Diseases.

We have before the committee, in addition to Dr. Fredrickson, the Director of the National Institutes of Health, Dr. Donald Whedon, the Institute Director.

Doctor, how would you like to proceed? Would you like to have your statement inserted in the record in its entirety, as if you had read it into the record, and then proceed with questions, or would you like to highlight it?

Dr. WHEDON. I would like to insert my statement for the record, Mr. Chairman, and then if I may, I would like to read a short form of it which would provide highlights.

Mr. NATCHER. All right, Doctor.

[The prepared statement follows:]

DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES

Mr. Chairman and members of the committee, I am pleased to have this opportunity to report to you on the programs of the National Institute of Arthritis, Metabolism, and Digestive Diseases, and to testify to the needs of these programs, especially for fiscal year 1977. As can be seen from the special reports which have been submitted to the committee, the past year has witnessed important advances in almost all of the areas of responsibility of this Institute.

These areas for which the Institute bears responsibility include arthritis and connective tissue diseases, diabetes and other metabolic disorders, digestive diseases and nutrition, diseases of the kidney and urinary tract, diseases of the blood, skin, and musculoskeletal system, and disorders of the endocrine glands.

In addition to meeting the challenge of responsibilities for these diverse and serious disease problems, constituting the widest span of categorical disease responsibilities at the National Institutes of Health, we shall be especially

mindful this year of the recommendations of the National Commission on Diabetes and of those soon to be submitted by the National Commission on Arthritis and Related Musculoskeletal Diseases. We shall, of course, do all within our budgetary and manpower resources to carry out their recommendations calling for increased and expanded efforts in these two disease fields.

Arthritis, Rheumatic Diseases, and Orthopedic Surgery

The report by the National Commission on Arthritis, among other findings, is expected to point out not only the suffering and disability of arthritis and rheumatism, but their serious and adverse effects on the economy.

Arthritis and rheumatism are terms that refer respectively to inflammation and destruction of joints and to disease affecting tissues surrounding the joints. Rheumatoid arthritis, the most crippling form of arthritis, continues to puzzle medical scientists. There is still no clear understanding of why one person develops the disease and not another, what triggers the disease to destroy normal joint tissue, and what causes it to progress.

A major thrust of our research will continue to revolve around the likelihood that rheumatoid arthritis is the result of an autoimmune reaction, in which the body overreacts to proteins originating within the body's own tissues. Such immune processes may be triggered by changes brought about by an infectious agent or agents.

In view of this real possibility, we have been following closely several recent studies of a body protein known as histocompatibility antigen W27, an inherited tissue component which "labels" the specific tissue type of individuals and which is found frequently associated with such arthritic diseases as ankylosing spondylitis (rheumatoid arthritis of the spine) and Reiter's disease (arthritis linked with inflammation of the duct which carries off the urine from the bladder and of the mucous membranes of the eyelids). An association has now been shown between this "label" sort of protein and another rheumatoid disorder, psoriatic arthritis, an arthritic condition associated with the skin disease, psoriasis.

This remarkable association of antigen W27 with these disorders suggests an inherited and common, increased susceptibility to a causative agent, possibly of an infectious nature. In the meantime, we are closely pursuing research into better treatment of the various forms of arthritis and related bone disease. In one such study, our grant-supported investigators have produced evidence of the value of needle aspiration in the treatment of septic arthritis (acute arthritis caused by infection of a joint), resulting in complete recovery in a significant number of patients.

Our investigators are also continuing their research on knee joint replacement with implanted artificial joints, following their earlier successes in the hip with this form of corrective orthopedic surgery for joints destroyed usually by osteoarthritis.

The Institute anticipates playing the lead role in implementation of the national arthritis plan, which is now being forged by the National Arthritis Commission, insofar as program authorizations and fiscal and manpower resources are provided.

Diabetes and Other Metabolic Diseases

We have long been aware of the scope of diabetes as a major health problem in the United States. We will, therefore, continue to focus on the basic questions about diabetes that must still be answered, including the mechanism of action of insulin, the intricate details of carbohydrate and fat metabolism that are deranged in the disease, and the precise nature of the blood vessel abnormalities characteristic of the disorder, which underlie the major complications of diabetes. High on our list of research interests in diabetes are studies on the pancreatic hormone, glucagon, which appears to be secreted in excessive amounts in diabetic subjects.

Experimental administration of another hormone, somatostatin, has been found to result in a lowering of glucagon levels. New evidence obtained in animal studies by our grant-supported investigators now shows that the development of diabetic hyperglycemia (excessively high blood sugar) requires the presence of glucagon as well as lack of insulin, and that glucagon suppression might help control elevated blood glucose levels in diabetes. In a related study by another of our investigators, it was found that suppression of glucagon secretion by soma-

tostatin prevents the ketoacidosis (a hazardous state of chemical imbalance which can lead to coma and death) associated with insulin deprivation in juvenile diabetes, thus providing further evidence of an apparently important role of glucagon in the development of this life-threatening condition which may periodically occur in severe diabetes.

The Institute anticipates playing the lead role in implementation of the national diabetes plan, recently submitted to the Congress by the National Diabetes Commission, insofar as program authorizations and fiscal and manpower resources are provided. We shall also pursue our research on a number of other metabolic diseases, including cystic fibrosis, a grave familial disease of children and young adults.

Digestive Diseases and Nutrition

The list of disorders of the digestive system is immense, afflicting more than 20 million Americans each year. These chronic and disabling diseases, including peptic ulcer, ulcerative colitis, and other disorders of the pancreas, gallbladder and liver, are complex disorders, both from the viewpoint of treatment by the practicing physician and from that of the biomedical investigator.

In connection with research related to peptic ulcer, one of our investigators has shown in preliminary clinical trials that cimetidine, a recently synthesized new anthistamine drug, is a potent inhibitor of gastric acid secretion in patents with duodenal ulcer. In studies thus far this agent apparently is not toxic and, so, may be useful in treating peptic ulcer disease.

Last year I reported that we have augmented our research attack on peptic ulcers by establishing a Peptic Ulcer Center in Los Angeles to launch a 5-year program involving 10 key investigators with multidisciplinary expertise who will study peptic ulcer from various approaches.

Similarily, we have now begun a 5-year study at 10 treatment centers across the country of the feasibility, effectiveness, and safety of dissolving gallstones with the aid of chenodeoxycholic acid given orally. In correlated work, our own scientists at our clinical research section in Phoenix, Ariz., have shown that chenodeoxycholic acid acts to reduce the ability of bile to produce cholesterol stones—and dissolve cholesterol gallstones—by decreasing the secretion, by the liver, of excessive cholesterol into the bile. It is suggested that low doses may be therapeutic or possibly preventive and without significant adverse effects.

We shall continue our programs in nutrition, one of the oldest areas of research of the Institute; today we are responsible for a large portion of such research supported by the National Institutes of Health and of the medically oriented nutrition studies supported by the Federal Government. Our program activities cover the full spectrum of nutrition research, from basic metabolic and physiologic studies to projects designed to determine how best to alleviate malnutrition and specific nutritional deficiency diseases.

Hematology

Studies of blood diseases represent an indispensable part of the Institute's research activity. The sum total of Americans afflicted with the killing and disabling disorders of the blood, excluding circulatory problems, but including the anemias and blood-clotting disorders such as hemophilia, is considerable.

In research related to Cooley's anemia, our Institute is supporting by contracts an intensive search for new iron-chelating (binding) 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. In the meantime, one of our grant-supported scientists has reported success with a newly devised technique for sampling fetal blood obtained at 20 weeks gestation from a fetus at risk for Cooley's anemia, and has predicted successfully that the child would be unaffected. Although more studies of the effectiveness and safety of this procedure are necessary, the study shows that prenatal diagnosis is rapidly becoming a reality for families at risk for offspring with Cooley's anemia and sickle cell anemia.

Urologic and Kidney Diseases

Urologic and kidney diseases are of prime importance, inasmuch as the latter group of disorders, including glomerulonephritis (Bright's disease) and nephrosis, kills an estimated 42,000 Americans each year. Treatment through a medi-

care-funded program of dialysis with artificial kidneys and of kidney transplantation, however, enable an additional 10,000 patients to be saved annually. Along with our concentration on studies of the nature and cause of the many different kidney diseases and on means of treating or preventing them, we are seeking to improve the use of kidney transplantation as a predictably successful and relatively permanent therapeutic measure against irreversible loss of kidney function.

Hand-in-hand with research which is intended to lead to prevention of kidney disease and kidney failure, we are making a major effort through our artificial kidney program to improve further the effectiveness of dialysis as a life-maintaining treatment for patients with irreversible kidney failure. Special efforts are devoted to obviate disabling and costly clinical complications of such an existence, and particularly, to decrease the high cost of dialysis treatment, most of which is borne by the Federal Government. Last year, I reported that our contract-supported scientists developed a device, an ultrafiltration cell, which removes excess sodium and water efficiently, rapidly, and inexpensively from fluid-overloaded patients on chronic hemodialysis. The investigators are continuing their studies of the cell, inasmuch as the new treatment can conceivably also be employed in other fluid-overload conditions such as chronic congestive heart failure, in lieu of currently used procedures which call for costly, prolonged hospitalization. Incidentally, an editorial in the prestigious New England Journal of Medicine called the new treatment for the management of fluid overload by the Institute-supported scientists a quantum jump ahead.

DERMATOLOGIC DISORDERS

Dermatologic disorders include psoriasis, a disfiguring disease which afflicts up to 4 million Americans and causes great mental anguish to its victims and their families. The cause of psoriasis is unkown, and the disease is marked by rapid proliferation and scaling of epidermal cells.

Current methods of management are generally unsatisfactory and certain drugs with a therapeutic potential have, also, unfortunately, caused serious side effects. We expect to continue our clinical evaluation of a new treatment for psoriasis involving an oral dose of a photoactive drug, methoxsalen, and subsequent exposure 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 for prolonged periods and its repeated use seems to be well-tolerated by the psoriatic patients who have been treated thus far. A long-term, Institute-supported study of the efficacy and safety of this new treatment is well along in its planning stage.

Finally, with pleasure and pride, I am happy to report to you two special awards to our investigators. One of our intramural scientists here in Bethesda, Dr. Bernhard Witkop, who as an organic chemist, collaborates frequently with Japanese scientists, has received Japan's second highest decoration for his scientific achievements. Also illustrative of the high caliber of our scientists was the 1975 Lilly award of the American Diabetes Association to Dr. Pedro Cuatreacasas, of Johns Hopkins University, for research he performed while an intramural investigator with our Institute.

In conclusion, Mr. Chairman, the budget request for the Institute for 1977 is $180,837,000. I shall be pleased to try to answer any questions and supply additional information desired for the record.

Mr. WHEDON. Mr. Chairman and members of the committee, I am pleased to report to you on the programs of the National Institute of Arthritis, Metabolism, and Digestive Diseases, and to testify to our needs, especially for fiscal year 1977. As can be seen from the special reports on research progress in specific disease areas which have been submitted to the committee, the past year has witnessed important advances in almost all of our areas of responsibility, including arthritis and connective tissue diseases, diabetes and other metabolic disorders, digestive diseases and nutrition, diseases of the kidney and urinary tract, diseases of the blood, skin, and musculoskeletal system, and disorders of the endocrine glands.

In addition to meeting the challenge of these diverse and serious disease problems, constituting the widest span of categorical disease responsibilities at the National Institutes of Health, this year we shall be especially mindful of the recommendations of the National Commission on Diabetes and of those soon to be submitted by the National Commission on Arthritis and Related Musculoskeletal Diseases. We shall, of course, do all within our budgetary and manpower resources to carry out their recommendations calling for increased and expanded efforts in these two important diseases.

A major thrust of our arthritis research will continue to revolve around the likelihood that rheumatoid arthritis is the result of an autoimmune reaction, in which the body overreacts to proteins originating within its own tissues. We have been following closely several recent studies of a body protein known as histocompatibility antigen W27, an inherited tissue component the presence of which coincides with that of several forms of arthritis. In the meantime, we are closely pursuing research into better treatment of the various forms of arthritis and related bone disease, including research on knee joint replacement with implanted artificial joints.

We have long been aware of the scope of diabetes as a major health problem in the United States. We will, therefore, continue to focus on the basic questions about diabetes that must still be answered, such as the mechanism of action of insulin, the intricate details of carbohydrate and fat metabolism that are deranged in the disease, and the precise nature of the blood vessel abnormalities characteristic of the disorder, which underlie the major complications of diabetes. We shall also pursue studies of other metabolic diseases, including cystic fibrosis, a grave familial disease of children and young adults.

The chronic and disabling digestive diseases, including ulcerative colitis, and other disorders of the pancreas, gallbladder and liver, are complex and widespread disorders. Peptic ulcer, alone, afflicts millions of Americans. In this area of research, one of our investigators has shown in clinical trials that cimetidine, a recently synthesized antihistamine drug, is a potent and apparently nontoxic inhibitor of gastric acid secretion in patients with duodenal ulcer. In gallstone research, we have begun a 5-year study at 10 treatment centers across the country of the feasibility, effectiveness, and safety of dissolving gallstones with the aid of chenodeoxycholic acid given orally. We shall also continue our programs in nutrition, one of the oldest areas of research of the Institute.

Studies of blood diseases represent an indispensable part of the Institute's research activity. Among our research goals is a definition of the specific defects which cause the various blood disorders, through the development of better knowledge of blood cell and blood component formation preparatory to development of improved diagnosis and therapy. In Cooley's anemia, for example, we are searching for new iron-chelating agents which could prevent the ultimately fatal iron buildup in tissues and organs of patients who must be kept alive with the aid of repeated blood transfusions.

Along with our concentration on studies of the nature and cause of the many different kidney diseases and on means of treating or preventing them, we are seeking to improve the use of kidney trans-

plantation as a predictably successful and relatively permanent therapeutic measure against irreversible loss of kidney function. Hand in hand with this research is a major effort by our artificial kidney program to improve further the effectiveness and reduce the cost of dialysis as a life maintaining treatment for patients with irreversible kidney failure.

Dermatologic disorders include psoriasis, a disfiguring disease which afflicts up to four million Americans and causes great mental anguish to its victims and their families. Clinical evaluation will be made of a new treatment for psoriasis involving an oral dose of a photoactive drug, methoxsalen, and subsequent exposure to ultraviolet light which appears to clear the skin lesions effectively.

I am happy to report to you that Dr. Bernhard Witkop, one of our organic chemists here in Bethesda who collaborates frequently with Japanese scientists, has received one of Japan's highest decorations for his scientific achievements. Also illustrative of the high caliber of our scientists was the 1975 Lilly Award of the American Diabetes Association to Dr. Pedro Cautrecasas of Johns Hopkins University, for research he performed while an intramural investigator with our Institute.

In conclusion, Mr. Chairman, request for the Institute for 1977 is $180,837,000. I shall be pleased to try to answer any questions and supply additional information desired for the record.

BUDGET CHANGES

Mr. NATCHER. Now, Doctor, your budget request for fiscal year 1977 is $180,837,000. I believe this is approximately a million over the 1976 obligation level. However, the budget justification material for your Institute shows a reduction of $6 million in research grants. Why such a large decrease in regular research grants, Doctor?

Dr. WHEDON. The explanation for that, Mr. Chairman, is that there are some alternations in some of the other lines in the budget—some of the funding proposed to carry through on centers has been increased. And there is an increase of about two and a half million dollars for our intramural research and other direct operations. Also, there is an increase of about $1,400,000 in contracts. And when those are added together and counterbalanced with the overall increase of about a million dollars, then to make it come out, the research grant line is reduced.

Mr. NATCHER. Doctor, to be frank, I don't know whether I am following you or not regarding these alterations. Isn't it more important that this money be used for the research grants than for the purposes that you say that you had to use this money, to bring about this reduction?

Dr. WHEDON. You may have misunderstood the word "alterations." I merely meant changes in where the money was placed in the budget.

Mr. NATCHER. I understand. Reshuffling.

Dr. WHEDON. All of the functions I mentioned are for research. They are just to be pursued through different mechanisms than by the research grant mechanism—by contracts, and research in our own laboratories in Bethesda, for example.

Mr. NATCHER. You feel then, Doctor, as far as research grants are concerned generally in your budget, we have an adequate amount before the committee. Is that the way you feel about it, Doctor?

Dr. WHEDON. We have money in our budget for research grants which will enable us to maintain a moderate level of continued activity. It is not ideal, by any means, but it will keep the operation going—not at the level we expect to do in 1976, however.

Mr. NATCHER. In other words, we are taking a step backward in fiscal year 1977; isn't that about right?

Dr. WHEDON. That is correct.

Mr. NATCHER. Which I think, is a serious mistake.

TRAINING PROGRAMS

The budget also shows a phaseout of the training grant program. Is this in keeping with the intent of the National Research Service Award Act, or is there some other reason for this phaseout of the training grant program?

Dr. WHEDON. It has been the intent for some time to gradually phase down and phase out the training grants program with the expectation that this function of training would be taken over by the National Research Service Awards. The emphasis in these new programs is in providing stipends to the individuals who will be learning how to cary out research, rather than in providing support to the institutions that would cary out their training. It is a difference in emphasis.

Mr. NATCHER. Your budget shows an increase in fellowship awards. The justification states that these fellowships will provide for doctoral training in specific shortage areas. What field, Doctor, will these individuals be trained for, and how did you identify the specific shortage areas?

Dr. WHEDON. In a series of programs such as we have, that are so broad, it is indeed very difficult for us to make judgments of this sort. I would say that we could not altogether make this judgment on the basis of actual shortages, but more on emphases that we believe should be placed on certain disease areas, and notable among these are diabetes, and also arthritis. The Diabetes Commission in its report, in effect says there are shortages in recommending more fellowships. I am fairly certain that the Arthritis Commission will make a similar recommendation.

DIABETES CENTERS

Mr. NATCHER. On page 151 of your budget justification, you failed to show how much of the proposed 1977 budget will be used to support the diabetes research and training centers, and the comprehensive arthritis centers. Doctor, if you will, tell us how much of the budget request will be used to support these activities.

Dr. WHEDON. In the budget that you have before you, there is no money for these centers. The President's budget for 1977 was prepared before the Diabetes Commission had completed its report. And hence, there was no inclusion of the recommended amounts for centers which the National Commission on Diabetes prepared and submitted in their report.

FIELD STATIONS IN PHOENIX

Mr. NATCHER. In your budget justification, you make reference to field stations in Phoenix, Arizona. What kind of intramural research are you conducting in these field stations?

Dr. WHEDON. This is the one field station we have. It is of two types. One is an epidemiology and field study operation with main laboratories in Phoenix, and an adjoining laboratory and clinical examination facility at the Indian Health Service Hospital in Sacaton which is about 40 miles away. Then also in the Indian Health Service Hospital in Phoenix, we have a clinical research unit of about 20 beds and associated laboratories. The program emphasis of both of these activities is the same. The primary focus is on diabetes, because the Indians, of the Pima Tribe in Arizona have a prevalence of diabetes 10 to 15 times the national average. So this represents an extremely good opportunity to concentrate our efforts on diabetes. The figure I would attempt to impress you with, Mr. Chairman, is that by the age of 50 years, half of the women in the Pima Tribe have diabetes.

Also in this area, we have a particular research interest in gall bladder disease, because there is a very high prevalance of gallstone disease among these Indians. And our other interest is in studies of arthritis of various kinds, spondylitis of the spine, and rheumatoid arthritis. The Indians in that area have a slightly higher prevalence of arthritis than the national average.

Mr. PATTEN. Mr. Chairman, our people go to Arizona to get cured of arthritis. They have been going to Phoenix and Tucson, and say it is good for arthritis.

Dr. WHEDON. I think the situation there with respect to our white Americans is that they feel better in Arizona than they do in New Jersey or New York.

Mr. PATTEN. The doctors told me they make their money on the easterners going down there to get treated for arthritis, who run into sinus trouble and that is their biggest practice.

Dr. WHEDON. I think that patients also tend to go there who have sinus trouble in the humid and dust-laden air of the East, as well.

I would like to tell you, Mr. Patten—if I may, Mr. Chairman—that this very point of the possible relationship of the environment, that is the physical environment, to arthritis, had been so much a part of our folklore—you know, that you have less arthritis in a hot dry climate—that we actually mounted a study about 12 years ago.

For this purpose we wanted to compare some well-defined population communities, one in a cold, wet area, versus a hot dry. So we studied the Blackfeet Indians of Montana, and compared them with the Pima Indians in Arizona. The prevalence of arthritis was almost exactly the same. But it paid off in that in studying the Pima Indians, we found this very high prevalence of diabetes, so we have stayed there to do our work now primarily on diabetes and gall bladder disease.

REPORT OF THE NATIONAL COMMISSION ON DIABETES

Mr. NATCHER. You referred to diabetes once or twice. I believe you have there on the table before you the report. Who is this report prepared by?

Dr. WHEDON. The report was prepared by the National Commission on Diabetes, which was established through an act of Congress in the summer of 1974.

The main section of the act required the establishment of a national commission and directed that it undertake efforts to prepare a long-range plan based on a careful study of the national situation with respect to diabetes.

A commission was appointed, had a series of meetings, and organized a number of work groups, each of which prepared written material in depth. What I am holding here is merely volume I. This is just the concentrated summary, you might say, of all their efforts, and contains their recommendations of what should be done in the future.

Mr. NATCHER. Doctor, I haven't had a chance to read volume I. But I am just wondering if in that summary somewhere, they won't say to you there is a whole lot more that should be done as far as diabetes is concerned at the national level. Do you have that anywhere in that report?

Dr. WHEDON. Yes. I can speak directly to it, if I may.

Mr. NATCHER. We would like to hear from you. You recall all last year and the year before last, we discussed this matter. We inquired as to what was being done as far as diabetes is concerned. The amounts requested in the main have been appropriated down through the years. Sometimes we have had increases, and the people want to know what is being done, why don't we move along faster.

Dr. WHEDON. The Commission, in reviewing the efforts of the National Institutes of Health, not only looked at our own Institute, which is the focal point of diabetes research, and has a strong intramural diabetes research activity, but they also looked at the extent to which many other Institutes support research diabetes—the Eye Institute, because of the obvious eye complications, the Heart and Lung Institute, Dental Research, Child Health, Neurological Institute, and so on, because of the various complications affecting many different organ systems. It also compiled a table which set forth recommendations for increases in the funding for support of research and training in these various fields.

They advised in particular for our Institute, in addition to an increase in funding that I have just mentioned for research and training, that there be established a Distinguished Scientist Training Award, so that there could be continued supervision of diabetes research by very well trained senior investigators.

Mr. NATCHER. Excuse me for interrupting—is that the proper procedure? You say a Distinguished Scientific Training Award. Is that good, Doctor?

Dr. WHEDON. Yes; I think that would be a very good thing to do.

Mr. NATCHER. All right. Go ahead.

Dr. WHEDON. Other recommendations for my own Institute are that there be established an advisory panel on transplantation research and on devices which could be devised to improve the continuing regulation of the blood sugar. They recommended that there be a special study of the effects of treatment in juvenile diabetes, in collaboration with the National Heart and Lung Institute, and that there be an improvement in the systems that we have for obtaining all sorts of information about diabetes, results of research and translation or trans-

mission of this information to practicing physicians, and to the general public. We have gotten underway to some extent in trying to follow out some of these recommendations even though the report was made only 7 or 8 weeks ago.

One of the particular areas that we are concerned with is the production of an artificial device which might improve the control of blood sugar, popularly called the artificial pancreas. We are in the process of putting together a system by which we can entertain applications for efforts in this regard, review them, and provide support. We actually expect to provide some contract support for activities of that sort in this fiscal year, 1976.

FUNDAMENTAL RESEARCH ON DIABETES

Mr. NATCHER. If I ask you what the Congress should do in conjunction with your Institute that would help more than anything else insofar as diabetes is concerned, what would you say, Doctor?

Dr. WHEDON. I think that the most important thing to do is to help us in our support for fundamental research studies of diabetes, because the cause of diabetes is not known. With regard to the metabolism or body chemistry of the disease, although a great deal is known, much more needs to be known. And we think in that way, in solid support of fundamental laboratory and clinical research, that we will eventually understand the disease sufficiently well that we will provide not only better care and control, but may actually one day come to the point of finding out how we can prevent the disorder.

Mr. NATCHER. How much of your budget would be tied directly to this goal?

Dr. WHEDON. The figure that I have for our diabetes studies in 1976 just directly related to diabetes is $14.7 million. And if one broadens that to include the related endocrinology and metabolic studies, the figure for 1976 would be $18.4 million. Now, the comparable figures in the budget before you, which you are considering for 1977, is $15.9 million for the diabetes program, and $19.6 million if one includes the closely related endocrine and metabolic basic fundamental research we are talking about.

Mr. NATCHER. You and I know that $19 million is a lot of money, Doctor. But insofar as the discussion we are having today, it is not much money, is it?

Dr. WHEDON. When you get right down to it, I think we could very sensibly put forth a greater effort.

U.S.–U.S.S.R. COOPERATIVE PROGRAM ON ARTHRITIS

Mr. NATCHER. We talked briefly with you last year about the cooperative United States and Soviet Union arthritic program. How is this program progressing, Doctor? Do we have anything other than what we discussed last year?

Dr. WHEDON. Quite a good deal has been done over the past year. There have been a number of visits of American experts in rheumatology and in orthopedics to the Soviet Union, and Russian scientists and clinicians have visited this country. We have worked out a cooperative research program in three principal areas.

If you would like, I could tell you just what they are. I think it would indicate the way in which we are planning to work rather closely together. The first area has to do with the evaluation of forms of treatment of various kinds of arthritis, medical forms of treatment, and specifically there is afoot a planned study of patients, both in this country and in the U.S.S.R., for the effect of a drug called penicillamine on adult rheumatoid arthritis, and then similarly, in a rheumatic disease called systemic lupus erythematosus, the effectiveness of two drugs in combination, which are called azathioprine and cyclophosphamide.

Then also under effects of treatment, there is particular concern for juvenile rheumatoid arthritis because of the severity of this form, and the likelihood there will be serious crippling deformity, so that a special joint study on juvenile rheumatoid arthritis will be conducted.

Also in a more fundamental direction, there is a program titled "Microbiology and Immunology of Rheumatoid Arthritis and Lupus," and in that program, there will be conferences from time to time between American and Russian scientists, exchange of data, and exchange of blood samples on patients, so that they can be examined in the same laboratory. The exchange of those blood samples has actually already taken place.

The third area is on the surgical treament of rheumatoid arthritis. This is where the orthopedic surgeons are involved. The Russians have gotten into artificial joint thereapy of osteoarthritis nearly as strongly as we have, and because of the important potential significance of this form of treatment, we are going to share experiences and do some joint studies in that area.

ARTHRITIS DRUGS

Mr. NATCHER. What progess are you making in developing an effective drug or drugs to ameliorate the symptoms of arthritis?

Dr. WHEDON. We are making really steady progress along those lines. One of the items I was going to mention was that there have been some recent studies on the effect of gold. Gold, of course, has been in use in the treatment of arthritis for a good many years—it must be 25 or 30 years at least, perhaps much longer. Because of the side effects, and the fact that it does not work in all patients, doctors are not uniformly for it, but recently, a careful study has been done which reconfirms the usefulness of gold. They found that it is particularly valuable in a way that was not suspected, in that it tends to prevent the destruction of cartilage and bone, which is a usual accompaniment to longstanding rheumatoid arthritis. In another study of the drug therapy of arthritis, investigators are now studying the effects of combinations of drugs.

One particular study with which we are familiar is a combination of cyclophosphamide, which is a sort of an anticancer drug, actually, in combination with prednisone, which is one of the cortico-steroids, and they find this combination works much better than either drug alone, and it is much better tolerated, because the side effects of the two compounds are different, and they can be given in lower doses much more effectively.

There is one other item, since we are talking about the treatment of rheumatoid arthritis, and that is that we have been continuously eval-

uating the effect of synovectomy—that is the surgical treatment of crippling arthritis, where the sheath of tissue that surrounds tendons and the linings of diseased joints, are removed, and we find this not only provides temporary help, but the inflammation tends not to return, if this inflammatory sheath or lining tissue is removed.

So we are, Mr. Chairman, making steady progress.

Mr. NATCHER. That is what you call the synovial tissue.

Dr. WHEDON. Yes; synovial tissue.

PSORIASIS TREATMENT

Mr. NATCHER. In your statement last year, you spoke about chemotherapy as a potential treatment for psoriasis, and you told us that it needed intensive controlled investigation for long-term effectiveness. This year you tell us the long-term study is in the planning stage. Are you going ot come back next year and tell us that the planning phase is just about finished? What about it?

Dr. WHEDON. Mr. Chairman, I would attempt to advance the time schedule from the implication of your question. We really are finished with the planning stage. We are about to let the contract for the support of the study of photochemotherapy, which I mentioned in my opening statement. This is an exciting new form of therapy. It will be conducted in 10 clinics, and over quite a considerable number of years, to determine the effectiveness and safety of this form of treatment.

But in addition to that, we actually have underway another, different kind of chemotherapy study for psoriasis, in which we are looking at a number of drugs which have been proven useful in the treatment of various forms of cancer, and testing out these various drugs on the skin, to see their effectiveness in reducing the rate of reproduction of skin cells, in the hopes that we shall come out with a very useful surface treatment of psoriasis by this means. So we actually have one project in being now, in action for the last 7 or 8 months, and another about to go any day now.

COST OF INSULIN THERAPY

Mr. NATCHER. We have had a number of people talk to us about the escalating cost of insulin. I realize that you have no control over the price charged by the drug companies. But are you conducting any research which could reduce the cost of producing insulin, or which would reduce the amount required by a diabetic?

Anything along that line, Doctor?

Dr. WHEDON. Yes, sir, we are. I speak in a slightly hesitant tone because I don't see the studies we are doing bearing fruit next week. I think they are going to be some time in coming. But as a result of fundamental studies which we supported, it was found that not only is a lack of insulin at fault in the development of high blood sugar in diabetes, but the presence in unusual amounts of another hormone from the pancreas called glucagon. So that one has to have not only insulin lack, but also excessive amounts of glucagon present to get into the hyperglycemic difficulties of diabetes, which may eventually lead to ketoacidosis, known popularly as diabetic coma.

Now, in conjunction with these studies of glucagon, another hormone originally found in a part of the brain, but now found to be in

other tissues, known as somatostatin, has been found to suppress the action of glucagon.

These studies have been done with intravenous infusion of somatostatin. It reduces this high blood sugar producing hormone, and prevents ketoacidosis. Now, it is a long way from that point to the end of the line. But the end of the line would be to have some form of somatostatin that would act for much longer than the very few hours of action that it has now, a long acting somatostatin that could be taken steadily and would provide hopefully a much more stable level control of blood sugar than we now have. So the answer to your question is a long yes, and with emphasis on the time involved.

FUNDING OF DIABETES RESEARCH

Mr. NATCHER. How much of the increased funds provided by this committee for your Institute for 1976 did you use to expand diabetes research?

Dr. WHEDON. In 1976?

Mr. NATCHER. 1976.

Dr. WHEDON. The diabetes program in 1976 was $14.4 million, and in 1976 it will be $14.7. So the increase really is very slight.

Mr. NATCHER. $200,000.

Dr. WHEDON. $300,000—which is very small.

NATIONAL DIABETES PLAN

Mr. NATCHER. In your opening statement you said you planned to play the lead role in implementing the national diabetes plan. I think generally you have given us a right good discussion now as far as the summary that you have before you, and other matters concerning the national diabetes plan. Would you like to add anything now other than what you have said to the committee?

Dr. WHEDON. I would like to say that we have undertaken some activities on our own which will, I think, increase our efforts in diabetes. For example, I was speaking a moment ago about glucagon. The investigator who has done the most work on that, who is really responsible for describing its importance in diabetes, is at the University of Texas. We are working out an arrangement whereby he and his group will spend some time in Phoenix and work in our laboratories there to take advantage of the opportunity with the Indians.

But speaking more directly to your question, I was a member of the national commission on diabetes, and so I participated in the discussions. I sat in on the work groups, particularly the one on research, as you might imagine, and I was impressed with the care, thoughtfulness, and the high quality of the discussion that went into the preparation of that report. So, I take quite seriously the recommendations of the commission and believe that they ought to be supported to every extent that we can with regard to our resources, both fiscal, and as far as manpower is concerned.

KIDNEY DIALYSIS COSTS

Mr. NATCHER. Last year, Doctor, you said that the kidney disease treatment program administered by the Social Security Administra-

tion would cost more, and that the costs would continue to go up. You certainly have been right about it. What progress are you making through your research to bring down the cost of kidney dialysis?

Dr. WHEDON. Over the course of some years now, we have been able to bring about changes in the devices and systems of dialysis, which have resulted in savings. We also were able to make it possible to do more hemodialysis in the home rather than the hospital, and that is a considerable saving.

Unfortunately, on that score, because of the way, as I understand it, that medicare, either the way that the legislation is written or the guide that medicare, either the way that the legislation is written or the guidelines or regulations are set, and the payment that stems therefrom to the patient, there is no encouragement to the patient to have his dialysis in the home, which is a relatively less expensive treatment, but rather to have it in a center or in a hospital, so that there are now fewer than 30 percent of patients having their dialysis done at home. I think the medicare system has been counterproductive in that respect, as far as reducing costs.

I would say, though, more directly on what we are doing, we are looking and are supporting a study on the effectiveness of shorter dialysis time—3 to 4 hours per dialysis versus the usual period of 6 hours. And if this is effective, this would be cost saving, because of the reduced amount of labor and overhead required in the treatment, and the possibility of treating more patients per costly shift.

Along this line, we are planning to put into effect a cooperative clinical trial on the effectiveness of various forms of dialysis treatment, and if we find one system is better than another, we shall, of course, recommend that, and that ought to be cost-saving.

ULTRA-FILTRATION CELL

Mr. NATCHER. Doctor, how far away are we from the application of the ultra-filtration cell that you pointed out in your statement? How far away are we?

Dr. WHEDON. Mr. Chairman, I wonder if I could defer to my associate director, Dr. Burton, who is directly in charge of the artificial kidney program and knows it very well.

Mr. NATCHER. Certainly.

Dr. BURTON. Mr. Chairman, if first I may reinforce what Dr. Whedon said earlier, this morning we received in the mail the most up-to-date report from the National Dialysis Registry, which we operate, and the percentage of patients who are being maintained on home dialysis has dropped to 24 percent, from a high point of 40 percent just before the medicare program. Thus Dr. Whedon's remarks concerning the downward tendency in home dialysis, are indeed justified to a strong degree.

Apropos the small devices which cause ultra-filtration of the blood and therefore can abstract fluid from the patient, these have already been used in a unique way in Montreal at McGill Hospital on an experimental basis. As you may recall, in his testimony last year Dr. Whedon mentioned the fact that serendipity is in action here. We, in experimental exploration of new ways of doing hemodialysis, developed these little devices that can take excess fluid out of the blood and

subsequently said they could also be used in other medical conditions where the physician would like to remove, either on an elective or an emergency basis, excess fluid from the patient. The first applications along that line have been taking place at McGill University. There a scientist who has been treating patients with so-called hemoperfusion, meaning the direct perfusion of blood through activated charcoal to purify it in renal failure, found that although he can remove some of the uremic toxins from the blood of the patient, he cannot remove any fluid, and these patients would not improve along that line, and their tissues would become edematous, or fluid-soaked. Subsequently he used these small blood ultra filtration units with success, and now uses them routinely. So that he has proven the point—from now on the possibility exists to use these devices in other medical conditions, where previously a patient would be admitted to the hospital for relatively long periods of time to reduce his fluid content with the aid of drugs and under close supervision. Now this can be done in a short period of time, quite safely, and relatively inexpensively.

Mr. NATCHER. Thank you, Doctor.

EMOTIONAL PROBLEMS OF DIALYSIS PATIENTS

Now, Doctor, as you and Dr. Burton well know, there are many problems other than the cost that confront the kidney dialysis patient, such as emotional problems, being kept alive by a machine. What are you doing now from this standpoint?

Dr. WHEDON. I am not sure we are supporting studies along those lines.

Dr. BURTON. We have in the planning stage a study of one of the greatest causes for emotional upsets in maintenance dialysis, and that is the sexual malfunctioning of the patient on dialysis. When we talk about the clinical long-term complications of maintenance dialysis, we usually mean such things as the anemia, which is quite debilitating, which keeps these patients in a fairly weak condition, we talk about bone lesions, and we talk about possible, though not very frequent, neuropathy, damage to the motor and sensory nervous system, particularly in the legs and arms.

The fourth complication, which most people usually don't talk about, but which is quite serious from the viewpoint of psychology of the patient, is the frequent impotence among male patients on maintenance dialysis, and impaired libido on the part of male and female patients. This is at the root of much of the psychological setbacks which patients have in that area. In our plans is a study to be started through a request for proposals along those lines, a study which really has never been carried out in a systematic fashion.

Mr. PATTEN. Mr. Chairman——

Mr. NATCHER. I yield.

COUNSELING OF DIALYSIS PATIENTS AND THEIR FAMILIES

Mr. PATTEN. In our hospital we have two kidney machines. Also there are our mental health facilities.

I personally saw the doctor charged with mental health responsibilities take a barber's wife and family in another room, to counsel them about their attitude, their behavior, and how to help the situa-

tion. I was told he spends time with the patient, too. I was a little surprised he would take that time, because he is a busy man. It may have been only this one instance, I don't know.

Dr. WHEDON. We are quite familiar with this matter, and it is indeed a very serious part of hemodialysis, artificial kidney treatment lasting over many years of time. The rate of depression, even despondency, is very high among such patients.

COOLEY'S ANEMIA

Mr. NATCHER. Doctor, how close are your scientists to developing an effective chelating agent to remore excess iron deposits from the vital organs of Cooley's anemia victims?

Dr. WHEDON. We now are supporting, through contracts, several studies directly along that line. The principal chelater, which is and has been under study with NIH funds, is a compound known as desferrioxamine, which has looked to be effective. Our Institute is now examining and testing other iron chelating materials, hopefully more effective. These need to be tested more carefully among our patients, and also in experimental fashion with animals, to see if they will work out. I would hope by next year we would be able to report and say we have made definite progress on that.

VINYL CHLORIDE AND LIVER DISEASE

Mr. NATCHER. Now, Doctor, I understand one of your intramural research projects concerns itself with vinyl chloride, which is associated with liver disease. What specific research are you doing in this area?

Dr. WHEDON. We have a study with which I am familiar, which is work that is being done by one of our investigators in our laboratory in Bethesda, in which he and his associates have been working on methods of protecting the liver; that is, being able to take over the function of the liver in detoxifying various serious and injurious agents. I am not certain that Dr. Berk is working with vinyl chloride, but I know he is working with compounds that are related to it in an effort to get at this problem.

TRAVEL COSTS

Mr. NATCHER. Doctor, in hearings with several of the other institutes we called attention to the fact that your travel cost averaged $642 per permanent position while those of the others are in excess of a thousand dollars per permanent position. Would you care to tell us how you managed to hold your travel costs down?

Dr. WHEDON. I would say that from my hearing of Dr. Rauscher this morning, that the big difference between the cancer program and ours, on a per capita basis with respect to travel has to do with the funds they spend to travel patients to Bethesda and back. We do not engage in that effort to anywhere near the extent that the Cancer Institute does. I think that is the main reason for the difference.

PERCENT OF GRANTS COMPLETED

Mr. NATCHER. This question, Doctor, you can answer for the record because I have consumed too much time.

What percentage of your regular research grants will reach their completion phase and thus not require continued support? How much in dollars will this amount to? You can answer that for the record.

[The information follows:]

Approximately 25.7 percent of the noncompeting research grants supported in 1976 were in their last year of committed support and do not require funds in 1977. These grantees may, however, again apply for support within the competitive system either for a new project or for a competing renewal of the same project. These completed grants had a value of $26,698,000 in 1976.

Mr. NATCHER. Mr. Michel.

Mr. MICHEL. Thank you, Mr. Chairman.

ARTHRITIS RESEARCH

Dr. Whedon, how much is included in your budget specifically for arthritis research?

Dr. WHEDON. The arthritis figure for that particular program for 1977 is $17.7 million.

Mr. MICHEL. What is that figure relative to last year?

Dr. WHEDON. In 1976, it is 16.7.

Mr. MICHEL. So there is a slight increase?

Dr. WHEDON. Yes.

Mr. MICHEL. Is any research being conducted elsewhere in the Federal Government on arthritis-related problems?

Dr. WHEDON. Yes. There is some arthritis-related research in several parts of the Federal Government. I think the one with which we are most familiar is the work in the National Institute of Allergy and Infectious Diseases. Immunity, or disordered immune mechanisms, is so high on the list of thought-to-be causes of arthritis, particularly rheumatoid arthritis, that the immunology-related studies of that Institute are extremely important. They regard them as definitely related to arthritis, and we think so, too.

Mr. MICHEL. Feel free to expand in the record on that.

Dr. WHEDON. I would like to tell what they do, for the reocrd.

[The information follows:]

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES ACTIVITIES RELEVANT TO ARTHRITIS RESEARCH

NIAID's involvement in immunologic and infectious diseases places its interest in the mainstream of research relative to problem areas of arthritis and connective tissue disorders. The Institute's primary responsibility for research on the immune system interfaces with the recognized thrust of arthritis research. Disorders of cartilage and synovial tissue of joints and the connective tissue of muscles and fascia are subject to involvement by immune and infectious processes.

Specifically, NIAID supports research and training in five special areas that have distinct relevance to arthritis and connective tissue diseases: Clinical immunology and immunopathology; immunochemistry and immune complex reactivity; basic biology of inflammation; infection and immunity; and immunogenetics—histocompatibility-ir gene associations.

I. CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY

NIAID's interest and concern in arthritis is a logical outcome of the identification of the specific disorders encompassed in this area associated with immunologic mechanisms. In the study of the rheumatoid process investigations have centered on the importance of antigen-antibody reactions and the pathology that arises from the deposition of the products of this reaction within the membranes

and cartilages of joints with subsequent initiation and maintenance of inflammation in these areas. Accordingly, NIAID grant support is responsible for research on the chemical characteristics of these antibody complexes, rheumatoid factors and especially those formed at the membrane surfaces of the joint. Also as a direct consequence of this Institute's in-depth involvement in the investigation of transplantation phenomena, immunosuppressive therapy has emerged. The application of information on the anti-inflammatory nature of these very same agents provides support for work bearing on the treatment of rheumatoid and immunologically related arthritides.

II. IMMUNOCHEMISTRY AND IMMUNE COMPLEX REACTIVITY

Studies effected by NIAID endeavors on the basic chemistry and biology of the generation and reactivity of immune substances have played an important part in demonstrating pathologic developments in autoimmune states. These are destructive processes that involve one's own joint and connective tissue as in systemic lupus erythematosus (SLE), amyloid disease, and sarcoidosis. Additionally NIAID's interest in hypersensitivity mechanims has in turn brought its allergic diseases program into the mainstream of autoimmune and SLE-like phenomena ensuing from specific drug reactions.

III. BASIC BIOLOGY OF INFLAMMATION

NIAID research has demonstrated the interplay of immune-induced inflammatory processes effected by humoral, chemical, and cellular mediators. NIAID-supported investigations are making it increasingly clear that aberrations and byproducts arising from the immune handling of microorganisms, foreign proteins, and injured tissue contribute to the intensity of joint and connective tissue inflammation by attracting specific cells with the capacity to effect inflammation. We appreciate that every effort should be made to develop correspondingly specific approaches to modulate the initiation of and to interrupt these tissue destructive processes. Accordingly, advantage is being taken of incoming basic information at molecular and cellular levels to encourage studies specifically concerned with target effects by looking at potentially effective drugs, agents, and techniques for immunosuppression.

IV. INFECTION AND IMMUNITY

NIAID's mission in infectious diseases has provided us with the opportunity for awareness of research developments that increasingly demonstrate that, even though invasion of joint and connective tissue by microorganisms may not be the leading cause of arthritis, the associations of infection and rheumatic processes are more than just coincidentally related. While microbiologists are looking at the biology of infecting organisms, NIAID-supported immunologists are examining host defenses for pertinent leads to understanding the equation. Especially important have been data generated from the study of viral and bacterial diseases, the chemistry of microbial autigens, the arthritic sequelae of streptococcal infection, and the definition of hypersensitivity inflammatory reactions induced by specific microbial agents and products. NIAID studies are finding evidence of secondary arthritic complications of gonococcal, mycoplasmal, and gastrointestinal infections.

One of NIAID's special emphasis programs on chronic and degenerative diseases of man deal with the enigma of "slow" and defective viruses. Here recent studies suggest that chronic virus infections may serve as initiating factors; for example, latency and persistence of measles virus and RNA tumor virus may be important in SLE.

V. IMMUNOGENETICS—HISTOCOMPATIBILITY-IR GENE ASSOCIATIONS

NIAID's interest in immunogenetics has emerged from its involvement in organ transplantation research and histocompatibility testing. Studies on individual genetic specificity, that is, the histocompatibility of cellular antigens, show that these may be important for predisposition to such arthritic and connective tissue diseases as rheumatoid arthritis, ankylosing spondylitis, and SLE. It should be noted that NIAID is the sole source of a complete panel of (HLA) typing sera that provides reagents to a large number of investigators studying the relationships between these genetic associations and rheumatic diseases. Accordingly,

we are sponsoring development of more efficient, precise and rapid techniques for these genetic identifications that will enhance the study of rheumatoid arthritis, its variants, SLE, and the arthritis accompanying psoriasis.

Dr. WHEDON. I would at the moment say that, as a part of the National Arthritis Act, there has been the creation of an arthritis coordinating committee which has put together all the agencies in the Federal Government, not just in HEW, that have anything to do with arthritis, and we have met and are in the process of preparing a report.

PROGRESS IN ARTHRITIS

Mr. MICHEL. Your statement seems to be pretty pessimistic about the progress in this battle against arthritis. Are we really making progress or kind of treading water?

Dr. WHEDON. I think we are making distinct progress. It is not the kind of progress that you might say is revolutionary or highly dramatic. I don't know whether you were here when I was describing some of the advances in the treatment of rheumatoid arthritis which I think are substantial.

I think one of the most interesting developments in just the last couple of years has been this matter of defining certain body proteins. The histocompatibility antigen that I mentioned in my opening statement, provides, you might say, a tissue typing of individuals. We find that the concentrations of these antigens are higher in patients with certain forms of arthritis than it is in the normal population, and by virtue of further pursuance of this effort, we may be able to define ultimately rather accurately the types of individuals who are susceptible to arthritis. After we reach that point hopefully we can find ways to prevent them from getting arthritis.

There has always been the suggestion that there may be some infectious agent, either a virus or some form of bacteria, which somehow gets into the body and ticks off this unfortunate and unwise immune reaction which leads to the development of the arthritis. If we can pursue that effort more strongly as well, to try to pin down what infectious agents might be the initiating impulses for this reaction, some day we may be able to develop a vaccine, you see, which will be useful to prevent certain kinds of arthritis.

Now in the popular press, particularly in recent months, there was quite a story about an arthritis vaccine and how effective it was. We have looked into that and can't get much substance to it at all. It was not done in a careful way and one always has to contend with the fact that arthritis waxes and wanes, and any improvement that you see, if it is not observed in a careful study, is most likely due just to the natural change in the course of the disease.

. Mr. CONTE. Would you yield there?

Mr. MICHEL. Yes.

GOUT

Mr. CONTE. Gout is a form of arthritis. Have they come up with any new medication to control it?

Dr. WHEEDON. Gout we now consider the most controllable form of arthritis that we have, and really nowadays anyone who has a diagnosis of gout ought to be well managed rather easily by means of the various forms of the drugs that we have now. It has been well worked

out that one can develop gout either through an overproduction of uric acid or through inadequate excretion, and there are drugs that work on both of those systems, so if doctors find out you are an overproducer, you take one form of drug steadily. If you have a renal excretion problem, you are maintained on another drug, and really, once that diagnosis is made, this may sound like a strong statement, but I really mean it, in most cases it is really well controllable.

Mr. CONTE. My father-in-law has it, and he is going through extreme discomfort with it and really has some bad problems. He can't seem to get it under control. This recent bout he had, they gave him so much medication, it affected his heart. That is why I was asking whether there was anything new in the area.

Dr. WHEDON. Well, of course the treatment of acute bouts is pretty rough, because colchicine causes a really severe diarrhea, in addition to the severe pain of the disease, itself. But once the acute attack is over, under normal circumstances, or in most cases I would say, unless there is some special problem of age or other condition, one would expect to be able to prescribe a drug treatment that would keep him from getting acute attacks again. You know, most of these patients have some little premonition that they are going to have an attack the day before. If he uses that signal and gets right to it with what his doctor tells him to take, he should be able to abort ever having an acute attack again. That is our attitude toward gout.

Mr. CONTE. That is good to hear. Thank you.

Mr. MICHEL. I was going to observe, if Henry VIII were living today, he would be a lot better off today than he was at that time.

SEPTIC ARTHRITIS

You make reference to the value of needle aspiration in the treatment of septic arthritis. What kind of treatment is this?

Dr. WHEDON. Septic arthritis is a very acute arthritis with infectious agents, usually bacteria, and I understand the treatment has been found is that if one puts a needle into the joint and withdraws that fluid and keeps replacing it with antibiotic preparations, that this has greatly increased the value of the treatment and is preferable to opening the infected joint surgically.

Mr. MICHEL. That has to be done on a regular basis?

Dr. WHEDON. It has to be continued. As I understand it doctors try to keep the joint dry and a high concentration of antibiotics in it and that seems to help take care of it.

TREATMENT OF PAIN

Mr. MICHEL. We hear about various types of treatment for normal types of arthritis, not in the advanced stage. Is there any one particular remedy that can help relieve the pain and discomfort, if nothing else?

The other day I heard, if my ears were hearing right, that for a headache one should take some arthritic pain reliever. In other words, take something stronger than a normal aspirin, I guess, for a headache. Here is something that is effective in arthritis, so take it for a headache.

Dr. WHEDON. The arthritis you are talking about are the aches and pains of every day?

Mr. MICHEL. You know how many times we get letters here, an elderly person will complain about their arthritic condition or their aches and pains and haven't been able to do this or that.

Dr. WHEDON. I think the thing to push here is aspirin, because aspirin is not only analgesic, has a pain-killing effect, but has an anti-inflammatory effect, so for moderate extent the pain in the joints or muscles is due to an inflammation, the aspirin will be effective.

Mr. MICHEL. So as a doctor who is directly working on it on a day-to-day basis, you would recommend it. I am inclined to think of the days in the service when you were on sick call and a doggone aspirin was good for everything, and they would send you back with an aspirin.

Dr. WHEDON. I would just add that it is also regarded as very important to keep up the mobility of the joints, and also heat. So heat, mobility, and aspirin are the three main features of keeping the joints reasonably happy.

DIABETES PROGRAMS

Mr. MICHEL. I notice the chairman was asking a number of questions with respect to diabetes. Did he ask you what in your budget was going for diabetes research?

Dr. WHEDON. Yes, he did.

Mr. MICHEL. OK.

How about in that area, other programs in Government, paralleling my earlier question. Rather than taking up the time, there must be some, and would you just simply spell it out in the record in something in telescope form from that report? Synthesize that or something for us, would you?

I guess, really, what I am interested in is generally in such and such an area, x millions of dollars are going for it. We get into so many of these categorical things here and debate on the floor and unless it is written out in this bill, they think nothing else is being done and sometimes we have to get together in five, six, seven or more places and say, actually, if you really want to know the total figure, here is where you have money, here, here, here, and here.

Dr. WHEDON. If I may just state briefly, Mr. Michel, what I am holding up is the first annual report to the Director of NIH of the Diabetes Mellitus Coordinating Committee, and this was created by the National Diabetes Act. I will submit a summary of this for the record.

Mr. MICHEL. Fine.

[The information follows.]

SUMMARY OF THE REPORT OF THE DIABETES MELLITUS COORDINATING COMMITTEE

This first annual report was designed to implement the first major objective of the Diabetes Mellitus Coordinating Committee by presenting a comprehensive review of all Federal programs now involved in diabetes or diabetes-related activities.

The following paragraphs summarize the major diabetes-related activities in the Federal health-related agencies.

Department of Agriculture

ACTIVITIES RELEVANT TO DIABETES MELLITUS

The major effort of USDA relevant to diabetes mellitus is intramural; it is performed within the Agricultural Research Service, as part of its research activities of human nutrition. These activities are not concerned with the pathology or therapy of the disease, but with the definition of human nutrient requirements which, when met, contribute to the maintenance of normal glucose metabolism. The Carbohydrate Nutrition Laboratory is studying the physiological effects of complex versus simple carbohydrates on intestinal absorption and on hormone levels as well as on the activity and induction of lipogenic and gluconeogenic enzymes. The Vitamin and Mineral Nutrition Laboratory is concerned with requirements for trace elements for the maintenance of normal glucose tolerance. The Lipid Nutrition Laboratory is concerned with the effects of diet on the lipid components of blood and tissues, mainly as they relate to atherosclerotic disease. Although this program is not directly related to diabetes mellitus, many of the parameters studied are of great importance in diabetics.

Department of Defense

ACTIVITIES RELEVANT TO DIABETES MELLITUS

The Department of Defense—DOD—does not currently fund or administer major research programs related to diabetes mellitus. DOD sponsors limited—(in-house) clinical research under its clinical investigation program—CIP. Current diabetes mellitus-related clinical research efforts under CIP are blood glucose controls in pregnant diabetic women, evaluation of infants of gestational diabetic mothers, and the role of the reninaldosterone system in the diabetic and correlations with nerve conduction and esophageal motility studies. DOD activities in the area of diabetes mellitus are primarily concerned with the provision of medical care to authorized beneficiaries. Since insulin-requiring diabetes mellitus is in general considered disqualifying for military service, diabetes mellitus is not currently one of the major health problems in active duty military personnel.

Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control

ACTIVITIES RELEVANT TO DIABETES MELLITUS

CDC does not have a program directly focused on diabetes. However, the broad range of CDC functions in prevention includes several areas which are both relevant and might be incorporated into diabetes prevention and control programs. On July 7, 1975, the Center made a presentation to the National Commission on Diabetes on sound prevention and control elements of a public health program focused on diabetes. Surveillance is one of the important functions of CDC which can well be related to the Diabetes Act provisions. Laboratory improvement is also a function which can contribute directly to diabetes prevention and control. The Center administers the Clinical Laboratory Improvement Act and promotes many general laboratory improvement efforts.

Food and Drug Administration

ACTIVITIES RELEVANT TO DIABETES MELLITUS

The Food and Drug Administration—FDA—is a regulatory law enforcement agency concerned with the protection of consumers. Although FDA does not have a specific diabetes program, certain activities of the agency are directly related to diabetes, primarily in the area of treatment. The Bureau of Drugs has the responsibility for assuring that drugs approved for use in the treatment of diabetes are safe, effective, and properly labeled. The Bureau of Medical Devices and Diagnostic Products is responsible for assuring that in vitro diagnostic products for diabetic patients are effective and properly labeled. The Bureau of Foods is developing new regulations for those special dietary foods designated as "low calorie," to assure that such foods do, in fact, have a low calorie content and are labeled appropriately.

Health Resources Administration

Activities related to diabetes mellitus

The Bureau of Health Manpower, Health Resources Administration, is concerned with determining the Nation's resources and requirements for health professions manpower through a variety of legislative authorities. Several Bureau programs have relevance for chronic illness, although they are not specific to diabetes. These are special projects intended to assist health professional schools to improve their curriculums; family medical residencies; area health education centers, manpower initiatives for special interprofessional training efforts to serve underserved areas in particular, long-term training, and research and development.

The National Center for Health Services Research does not have any diabetes specific grants, projects, or contracts.

The National Center for Health Statistics is responsible for information dissemination through its many publications. Much of the statistical information is derived from the health interview survey. The latest HIS for which diabetes-related data are available in 1973. HIS data furnish prevalence and demographic information on the diabetic population.

Health Services Administration

Activities relevant to diabetes mellitus

The Health Services Administration is composed of four bureaus including the Bureau of Community Health Services, the Bureau of Medical Services, the Bureau of Quality Assurance, and the Indian Health Service. Each bureau conducts some activities relevant to diabetes mellitus. The agency's interest in diabetes relates primarily to the fact that this is a disease entity that affects, to varying degrees, the populations served by our programs, particularly the American Indians.

National Institutes of Health

National Institute of Arthritis, Metabolism, and Digestive Diseases

Diabetes research at the National Institutes of Health is centered in the National Institute of Arthritis, Metabolism, and Digestive Diseases—NIAMDD. In addition to its intramural laboratory and clinical research in Bethesda, Md., the NIAMDD supports through its research grants program more than 150 different research projects related to diabetes at various nongovernmental institutions across the country. In addition to these projects directly or primarily concerned with diabetes, other research performed or supported by the Institute involves the disciplines of endocrinology and metabolism which are related closely to diabetes.

Institute research is focused principally upon efforts to find a cure or to identify a means of preventing the devastating long-term complications of diabetes. Approaches to the many problems of this complex metabolic disorder take many forms. For instance, there are structure-function studies of insulin and glucagon, studies of carbohydrate metabolism and lipid metabolism, studies of the mode of action, mechanism of release, secretion and biosynthesis of hormones and other metabolic products, and support of a selected number of diabetes-endocrinology centers. Other important research areas include epidemiological studies of the Pima Indians of Arizona, development of several new therapeutic approaches (now in the experimental stage in animals), and monthly publication of the Diabetes Literature Index.

The NIAMDD, principally through its Associate Director for Diabetes, Endocrine and Metabolic Diseases, will be the focus for coordination and implementation of the recommendations of the National Diabetes Commission.

National Eye Institute

Because of the serious effects of diabetes on the eye, the National Eye Institute (NEI) places major emphasis on diabetes-related vision research. Investigations supported and conducted by the Institute are aimed at reducing the rate of blindness and visual disability from this disease. The NEI currently allocates 14 percent of its grants and contracts research budget to this effort by fostering laboratory and clinical investigations of diabetes-related eye

problems and by supporting the development and evaluation of new treatment procedures. A major portion of this research is concerned with diabetic retinopathy, the most serious and common visual problem arising from diabetes and one of the leading causes of blindness in the United States.

National Heart and Lung Institute

While the National Heart and Lung Institute (NHLI) does not have a direct programmatic focus on diabetes, it does support investigations which are diabetes-related. The metabolic effects and cardiovascular consequences of diabetes are studied as aspects of NHLI-supported investigations focused on atherosclerosis, hypertension, coronary heart disease, peripheral vessel disease, arrhythmias, heart failure, shock, and thrombosis in man and animals. In addition, epidemiological investigations of coronary heart disease include studies of diabetes as one of the several predisposing risk factors.

National Institute of Child Health and Human Development

Most of the activities conducted by the National Institute of Child Health and Human Development (NICHD), with primary relevance to diabetes, deal with diabetes in pregnancy and the influence of this disorder on the mother, the fetus and the newborn, and with the influence of age on carbohydrate metabolism. In addition, NICHD conducts other projects which are somewhat less directly related to diabetes. Although the main focus of these projects is in other areas, some aspects of the research are relevant to the study of diabetes mellitus. Some of the topics of concern in these projects are as follows: metabolic and hormonal influences on carbohydrate metabolism in infants or diabetic mothers and low birth weight infants; pathophysiology of hypoglycemic disorders; and adipose tissue metabolism in obese, nonobese and diabetic subjects.

National Institute of General Medical Sciences

The National Institute of General Medical Sciences (NIGMS) supports research in the basic or general biomedical sciences which have significance for two or more institutes. Research relevant to diabetes would therefore either be of a kind also relevant to other categorical interests and diseases, or serve as a type example illustrating or helpful in elucidating general biological principles. The Institute support in this area is exclusively extramural, through grants (including center grants) and contracts and is distributed among the five program areas: pharmacology-toxicology, clinical and physiological sciences, genetics, cellular and molecular basis of disease, and biomedical engineering.

National Institute of Neurological and Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) conducts and sponsors basic, clinical and applied research as well as research training, in the causes, prevention, diagnosis and treatment of toxic, metabolic, endocrine, deficiency, cerebro-vascular, cardiovascular and reno-vascular disorders which have direct bearing on understanding the underlying physiopathogenesis of diabetes and its complications in the central and peripheral nervous system.

National Institute of Dental Research

The National Institute of Dental Research (NIDR) is concerned with diseases that are specific to the oral cavity and systemic diseases that have manifestations in the mouth. The Institute is interested in diabetes mellitus, primarily in terms of its effect on the oral cavity. Diabetes is not one of the Institute's major areas of emphasis, but the etiology, pathogenesis and clinical manifestations of this disease are of interest to several of the major program areas within the Institute, including collagen research, the relationship between diabetes and peridontal disease, developmental biology and anomalies, caries, and diseases of the salivary gland and pancreas.

Social and Rehabilitation Service

Activities relevant to diabetes mellitus

In its capacity as a financing agency for medical care for the needy, the Medical Services Administration of SRS does not administer any project grants or contracts specifically focused on diabetes.

SOCIAL SECURITY ADMINISTRATION

ACTIVITIES RELEVANT TO DIABETES MELLITUS

Due to the wide range of activities supported by the Social Security Administration, specific data on the agency support of diabetes-related activities cannot be readily identified. However, the Social Security Administration is responsible for the publication of certain information on chronic diseases and disability, including diabetes.

NATIONAL SCIENCE FOUNDATION

ACTIVITIES RELEVANT TO DIABETES MELLITUS

Historically the National Science Foundation does not support medical research per se, though many basic research projects for which the Foundation does provide support have aspects or produce knowledge of interest and utility to researchers in applied medical areas. In areas related to the acquisition of knowledge that may have bearing on diabetes mellitus, several types of effort may be identified from the list of projects provided. For example, a substantial number are concerned in various ways with the synthesis or degradation of a variety of carbohydrates or lipids or other body components, especially as that activity may be controlled through hormones or medicated through enzymes. Other projects are directed toward increasing our understanding of the mechanisms involved in secretion and utilization of insulin. And a few treat the transport of sugars within cells or through membranes.

VETERANS ADMINISTRATION

ACTIVITIES RELEVANT TO DIABETES MELLITUS

In fiscal year 1973, the VA research program provided funds in the amount of $2,428,905 for support of 162 projects which were related primarily to diabetes research, and $1,154,661 for an additional 194 projects which were diabetes-related, but in which diabetes was not the primary focus. Because of the size and complexity of the VA medical care program and the large number of diabetics who receive VA medical care, it is not possible to summarize these activities in the space allotted.

CYSTIC FIBROSIS

Mr. MICHEL. How about cystic fibrosis? How much in your budget for cystic fibrosis?

Dr. WHEDON. In this year's appropriation, 1976, it is $2.9 million, and in our budget for next year, we are forecasting $2,788,000.

Mr. MICHEL. While we are on that subject, isn't there at least one other institute out there at NIH that would have something to do with respect to cystic fibrosis research?

Dr. WHEDON. The Allergy and Infectious Disease Institute is interested in the infectious part of it because of the pulmonary infections and also the Heart and Lung Institute; they support the pulmonary centers for that disease.

HEMOPHILIA

Mr. MICHEL. Now, how much of your budget goes for hemophilia, or is that possible to break out in a specific figure?

Dr. WHEDON. I think that hemophilia is supported through the programs of the National Heart Institute. In our intramural research program we have a hemotology coagulation laboratory which is one of the leaders on various problems of bloodclotting, but as far as support of research on the outside of coagulation disturbances, the Heart and Lung Institute covers that.

Mr. MICHEL. Dr. Whedon, I guess you weren't here this morning.

Dr. WHEDON. I was here.

PEER REVIEW PANELS

Mr. MICHEL. I mentioned the list of questions with respect to peer review panels, et cetera. I am not going to repeat those, but simply submit them for the record at this point, and if you will respond then for the record. We will do that for every Institute to try to keep it as similar as we can, one Institute after another.

[The information appears under the Office of the Director testimony.]

Dr. WHEDON. If I could just say briefly, our activity is very small in that respect. We have a total contract program of only about $8 million altogether.

Mr. MICHEL. Would that be the lowest of the institutes, do you know?

Dr. WHEDON. I am not sure of that, but I think it vies for that position. The bulk of our supportive research is by the research grant mechanism, which is reviewed by the Division of Research Grants at the first level, and then comes to our National Advisory Council for a final judgment.

Mr. MICHEL. Thank you.

PRIORITY OF MEDICAL RESEARCH

Mr. NATCHER. Mr. Patten.

Mr. PATTEN. Doctor, do you know how much we spent in this country last year for perfume?

Dr. WHEDON. I have no idea, sir, but I am sure it is a large amount.

Mr. PATTEN. Do you know how much we spent for booze? I will give you a hint. We collect $10 billion in taxes on it.

Do you know how much the women spend for the beauty shops of America? Do you know how many times it is your budget?

Dr. WHEDON. I am impressed. Without knowing the figure, I am impressed.

DIABETES

Mr. PATTEN. We have a wonderful country. Do you know what we did last year? We shipped $35 billion worth of guns to other countries. I was at a place Saturday night and the fellow who played the piano had gone blind from diabetes. He was an engineer and at 35 he lost his eyesight. He said, "My mom died from it, and that is what caused my diabetes."

You never mentioned the word "heredity." I have heard "heredity" all my life, and I don't think you mentioned it.

Dr. WHEDON. No, I didn't mention it, but it is properly mentioned in conjunction with diabetes. There is a tendency for diabetes to run in families. The actual genetics seemed to be all well worked out at one point and now we are not so certain. But there is a tendency for the susceptibility for diabetes to continue to run in the family.

ARTHRITIS

Mr. PATTEN. I don't remember your saying anything about years of age in regard to arthritis. Are the Indians that have arthritis out in Phoenix elderly?

Dr. WHEDON. No; as a matter of fact, they have a considerable shortened life expectancy, which one would suspect since so many of them have diabetes in association with gallbladder disease.

Mr. PATTEN. I had always thought arthritis was a disease from growing old.

Dr. WHEDON. Actually, there are probably 100 different varieties of arthritis and most of the time we speak of just the very common kinds that I have spoken of today, rheumatoid arthritis, which is the severe crippling kind that can occur in childhood but more commonly occurs in the forties and then thereafter. Osteoarthritis is the one that is most likely associated with advanced age, and we spoke of gout. But there are several other kinds, and they all have different ages of onset and different characteristics.

PSORIASIS

Mr. PATTEN. Skin specialists over the years never would admit the relationship of fat to psoriasis. Now they are advertising, "Go to Israel and get rid of psoriasis." You can do that in the gym here. We have an ultraviolet lamp down there. You don't have to go to the Dead Sea.

Dr. WHEDON. What you raise, Mr. Patten, is quite interesting in relation to the photochemotherapy that I was talking about. It is a combination of a drug that you take by mouth and then 20 minutes or half hour later, you are exposed to this ultraviolet light, but it is not an ordinary ultraviolet light that does it. It is a special long wave ultraviolet light. It so happens that in Israel when you get down by the Dead Sea, the rays from the sun have been altered so that you get this same long wave ultraviolet light at the Dead Sea, that you have with these lamps.

Mr. PATTEN. Millions have arthritis and psoriasis, and I had always associated it with age and heredity, but, as you say, you are not making any dramatic breakthroughs and even the budget, on the dollar sign they are standing still, aren't they?

Dr. WHEDON. That is right, Mr. Patten.

Mr. PATTEN. I wonder if we could have the public list what they spend. What do you think we spend for gas and oil in our automobiles? Think of our priorities in America. People will do what they want to do when it comes to smoking, drinking booze, and using perfume.

I see poor people with diabetes and arthritis and psoriasis and other diseases. Cystic fibrosis was covered here quickly. I am part of the crowd that joins the drive every year, and have for many years, to raise a couple of dollars in the area. We only have 50 cases in the county maybe. We get our share of kidney troubles, and that hits you hard.

KIDNEY DIALYSIS UNDER SOCIAL SECURITY

We passed H.R. 1 and you get a lot of money, I think, out of the Social Security money. Would you have any comment about our HEW bills that allow Social Secrity benefits to pay for a dialysis machine? Have you any comment about that, Doctor? Is that all right; is it good; should we repeal it, modify it?

Dr. BURTON. I think that the legislation and the voting on it showed it probably reflected popular sentiment. It is an expensive proposition,

which is likely to rise each year for the simple reason that one part of the treatment, dialysis, must be continued for the life of the patient, and each year new patients require treatment.

COST OF KIDNEY DIALYSIS

Mr. PATTEN. When I had a man who wanted to pay for two dialysis machines, the hospital director said "I need $50,000, another room, and a doctor and nurses," and he quoted a price tag of $50,000.

Dr. BURTON. He is correct. That is within the range that would be needed to make those two machines work full time for patients. If I may address myself to that, most of the money we spend in our Institute on kidney-related research goes not so much for improvements in the end stage kidney disease, but goes for basic research to prevent these diseases in the first place, so people don't end up with end stage kidney disease. All of us hope that one of these days—and it is a complex mechanism that underlies some of these diseases—we will be able to either treat people sooner and more effectively or prevent the disease outright, so that the number of people who need artificial kidney machines will be much smaller.

Mr. PATTEN. Doctors, we wish you luck and we feel that the work the Institute is doing is very important.

Dr. WHEDON. We appreciate that very much, Mr. Patten.

Mr. NATCHER. Mr. Shriver?

CYSTIC FIBROSIS

Mr. SHRIVER. Thank you, Mr. Chairman.

I think Mr. Michel asked you about cystic fibrosis, the amount of money allowed in this budget, and you said something like $2.7 million.

Is that all you will use in grants for outside research on this problem? That isn't very much money.

Dr. WHEDON. Our Institute has an intramural research laboratory headed by Dr. Paul di Sant'Agnese, in Bethesda, who works on cystic fibrosis, but the majority of the money does go out in support of research grants. It is all for research.

Mr. SHRIVER. One sentence in your statement kind of pinpoints the matter. You say it is "a grave familial disease of children and young adults." Is that as long as they live?

Dr. WHEDON. The life expectancy has been lengthened, but it still is a disorder of children and young adults. Five years ago we would have said it is a disease of children and stopped there.

Mr. SHRIVER. So some progress is being made.

Dr. WHEDON. Some progress is definitely being made. The clinical management of the disease has improved. I could cite a couple of incidences of things that we have done just in the last year, or supported.

One has been to detect that in the stools of newborn infants, a certain enzyme is increased in babies that are going to develop cystic fibrosis. So this would be a means of detecting cystic fibrosis immediately after birth, or very, very early. This is a test that can be used, and if so, then that child could be watched and protected and given treatment at the very earliest possible time. So that is one recent development.

Another which is less dramatic, I think, is that Dr. di Sant'Agnese and his associate, who is now in the Child Health Institute, has found that there is a certain protein in the blood called polyamines, which are decreased in individuals who are carriers of cystic fibrosis.

Mr. SHRIVER. So there is another institute involved, and other money being spent?

Dr. WHEDON. The extramural program or grants are entirely from our Institute. There is an investigator in the other Institute who used to be in ours, who is also working on cystic fibrosis.

GALLSTONE STUDY

Mr. SHRIVER. In your statement you mentioned the 5-year study at 10 treatment centers in the country of the feasibility, effectiveness and safety of dissolving gallstones.

Dr. WHEDON. Yes.

Mr. SHRIVER. Where are those centers? Would you put that in the record?

Dr. WHEDON. I would have to do that. The supervising center where the statistics are managed is at Cedars-Sinai Hospital in Los Angeles.

[The information follows:]

The ten treatment centers in the cooperative clinical trial on dissolution of gallstones are:

Scott & White Clinic, Temple, Tex., Emory University Hospital, Atlanta, Ga., San Francisco General Hospital, San Francisco, Calif., Duke University Medical Center, Durham, N.C., Mayo Clinic, Rochester, Minn., Cedars-Sinai Medical Center, Los Angeles, Calif., Cornell University, New York, N,Y., University of Pennsylvania, Philadelphia, Pa., Yale University Hospital, New Haven, Conn., University of Minnesota, Minneapolis, Minn.

Mr. SHRIVER. Are they all doing the same thing?

Dr. WHEDON. They are working under the same protocol so that by the concerted effort of the 10 clinics there will be a satisfactory number of patients who have been treated the same way so that a proper evaluation can be made of the effectiveness of the treatment and its safety, as well.

REDUCING COSTS OF KIDNEY DIALYSIS

Mr. SHRIVER. You mentioned that special efforts under urologic and kidney devices are devoted to obviate disabling and costly clinical complications of such an existence, and particularly to decrease the high cost of dialysis treatment.

What efforts are being made on reducing the cost of dialysis?

Dr. WHEDON. I did speak of that, Mr. Shriver, but in a word we spoke of the continuing effort of improvement of the kidney machines and of the system of administering this treatment. Of particular interest to us now is the likely cost-effectiveness of reducing the time of dialysis from the usual 6 hours to 3 to 4 hours.

Mr. SHRIVER. Is that being followed now?

Dr. WHEDON. No, I would say not. This reduction in time is being tried in a few places and in order to find out whether it is truly effective or not, we are beginning a study in several different hospitals to evaluate this treatment. It is a planned, highly organized study to see how effective this treatment is.

1977 BUDGET REQUEST

Mr. SHRIVER. Doctor, you are asking in this request for a little over $180 million. How does that compare with the other Institutes, say, Heart and Lung, and Cancer?

We haven't been increasing this Institute as much down through the years as we have the others, have we?

Dr. WHEDON. That has been my impression, particularly in thinking of all the responsibilities that we have, the many different categorical diseases for which we are responsible. The Cancer Institute has the largest budget and Heart and Lung Institute is second, followed by the National Institute of General Medical Sciences, and then the Arthritis, Metabolism, and Digestive Diseases Institute comes in.

Mr. SHRIVER. I agree with you, Mr. Patten, that this certainly is an area that affects about everybody in the country.

Mr. PATTEN. They have a budget around $2 billion. We are talking about less than $200 million. You are less than 10 percent of this budget.

Mr. SHRIVER. The enormity of the need is staggering.

Dr. WHEDON. I agree, Mr. Shriver.

Mr. SHRIVER. I commend you. Thank you.

Mr. NATCHER. Mr. Roybal?

SUFFICIENCY OF FUNDING

Mr. ROYBAL. I am concerned also about the fact that last year you received $178.9 million; that this year you get an increase to $180.8 million. This does not take care of inflation. It is my understanding that you have additional programs and recommendations that have to be implemented and so forth. How can you do all of these things with the request that you are making?

Dr. WHEDON. The answer simply is that we cannot.

Mr. ROYBAL. The answer then is that the moneys made available for the work that you want to do is not sufficient to cover the needs as you see them for this coming year?

Dr. WHEDON. That is correct. I would make this modification, that the budget that you see before you was prepared before the submission of the report of the National Commission on Diabetes, but on the other hand in addition to this, we are expecting a report from the National Arthritis Commission toward the end of April which will place additional demand on our resources and manpower.

NATIONAL COMMISSION ON DIABETES

Mr. ROYBAL. Aren't you telling this committee, then, that you really don't have a plan to implement the recommendations of the National Commission on Diabetes as of the moment?

Dr. WHEDON. We are getting underway to the extent that we are able to.

Mr. ROYBAL. Yes, but to what extent? You have some excellent recommendations made by the National Commission.

Dr. WHEDON. I would give you an example. The National Commission recommends the establishment of research and training centers.

Mr. ROYBAL. Do you agree with that?

Dr. WHEDON. I agree with that recommendation. We have already gotten underway to draw up the guidelines for the preparation of applications, receipt of applications, review, and the administration of the centers' programs, but there is nothing in our budget that would support them.

Mr. ROYBAL. How much time was spent by the members of the National Commission in preparing this report, and how much money was spent in making it available, and then once it is made available, what good is it if you can't implement its provisions?

Dr. WHEDON. The National Diabetes Commission had its first meeting in March of 1975, and completed its report and submitted it to the Congress on December 10. The total expenditure of the Diabetes Commission not only of its meetings, but all the work groups that also met to provide them with advice, for personal services, and travel and subcontracts, was $815,000.

Mr. ROYBAL. That was the total amount spent?

Dr. WHEDON. That is the total amount because the Commission is no longer in existence.

Mr. ROYBAL. And they provide you with a printed report and that is included in the $815,000?

Dr. WHEDON. That is right.

Mr. ROYBAL. So what we got out of it is a nice printed report?

Dr. WHEDON. And recommendations for what should be done.

Mr. ROYBAL. Well, that is what I am afraid of. We get all kinds of fancy recommendations, and no one does anything about it. I have the same concern as Mr. Patten and others, that while we have the expertise to implement recommendations made, and desire to do something with it, we don't move along because of finances. Your budget clearly indicates that we are not going to have any implementation of recommendations made.

Dr. WHEDON. You have understood the situation correctly.

FUNDING OF ARTIFICIAL KIDNEY PROGRAM

Mr. ROYBAL. Does it also indicate that the artificial kidney program, dialysis, and so forth will remain at a standstill because of the fact that we are not providing sufficient funds for it?

Dr. WHEDON. The situation is a bit different with respect to the artificial kidney program. I think that we have been making good, steady progress at the rate of about $41½ million a year. Of course, it has not been that same figure each year, but that is the current level of the program, and I feel with approximately that level of support, we can continue to make reasonable progress.

DHEW BUDGET PLAN

Mr. ROYBAL. One last question on the same subject. Where did this figure of $180.8 million come from? Was that your recommendation?

Dr. WHEDON. The origin of the figure is that we were originally given a ceiling under which we might be expected to operate in fiscal 1977.

Mr. ROYBAL. Who gave you that ceiling?

Dr. WHEDON. That was presented to us through budget channels from the Department. Actually, the ceiling was $1 million higher than that.

Mr. MILLER. If you look in this year's budget you will see figures in there for the Department of Health, Education, and Welfare for 1978. It is in the budget now. That is our starting point. That ceiling will change throughout the year as the institute makes recommendations and they are passed on to us and we in turn give them to OMB, but that is the starting point.

Mr. ROYBAL. I really don't understand. You say that is the starting point; starting point for what?

Mr. MILLER. For the whole Department's budget and that includes all our items, social security and public assistance and everything else. We have to figure out if we had to live in that ceiling how much would we suggest we spend on health, and how much on education, et cetera.

Mr. ROYBAL. But it is still an imposed ceiling.

Mr. MILLER. Yes; a Presidential ceiling.

Mr. ROYBAL. It is not one based on need and on recommendations made by experts in the field.

Mr. MILLER. No; we have not been able to budget for years anything that represented what we could put to good use.

ABSENCE OF SCIENTIFIC INPUT

Mr. ROYBAL. So, we can safely assume that the ceiling finally reached upon was made by accountants with very little attention given to the recommendations of scientists and the medical profession.

Mr. MILLER. I must object to the word "accountants." It was made by people who have to look at the economic situation and make political and policy decision.

Mr. ROYBAL. People who are expert in the field of finances?

Mr. MILLER. It is much more than finance, as you are aware. It is economics, politics, and the whole works.

Mr. ROYBAL. That is exactly what I am worried about, that it is based simply on politics and that the real needs of the American public are not really being addressed when it comes to the presentation of the budget.

Mr. MILLER. I would submit choosing your priorities and deciding on the budget ceilings does take into account the real needs of the American people.

Mr. ROYBAL. The priorities then are not chosen by those individuals who are actually doing the job of trying to deliver to the people of the Nation certain health facilities. That, I think, is more important than looking at this from the standpoint of politics and dollars and cents.

My background is accounting, and I know a little bit about figures. I am not half as knowledgeable as you, but I also know the political field. And I just don't like to see a budget being imposed upon experts who in turn will tell you that more money is needed and that the problem is such that the whole Nation is going to suffer if they don't get it.

On matters of priority, I would rather have money spent for this Department than to have money spent on sophisticated military weapons that we don't need anyway. I agree that we need a strong country and must be at all times on the alert, but I still maintain that there is a great deal of money being spent because certain generals like to see sophisticated military equipment displayed on the 4th of July.

That is an exaggeration, of course, but I am trying to make the point that we should start paying more attention to the health needs of this Nation. It seems to me that when a budget is prepared, we should start by listening to our experts who deal with the problem daily.

That is all, Mr. Chairman.

Mr. PATTEN. May I ask a question?

Mr. NATCHER. Go ahead, Mr. Patten.

QUALITY OF HEALTH CARE SYSTEM

Mr. PATTEN. Doctor, we are forever making comparisons with Sweden, Ireland, Germany, and the like, and, as you know, there are two sides to the coin.

Doctor, when all is said and done in this Bicentennial Year, as you look around the world at Japan, at West Germany, France, the rest of the civilized world, if you are going to compare our effort in your work for the general good of our people, have we a right to feel proud as Americans?

Dr. FREDERICKSON. Could I answer?

Mr. PATTEN. Sure, you are the expert. How about the Russians? They have socialism. Somebody up there says, "No more Vodka." He can issue a decree. Under our free society can we do as well?

Dr. FREDERICKSON. I think we can do as well. We don't have complete data but I think the American people have been about as generous and careful regarding medical research, per capita, as any country in the world. They have given us a strong apparatus for the development of new knowledge for the betterment of mankind.

Our job is to keep it strong and make it work as efficiently and effectively as we can. We have tough priority decisions to make. There will never be enough for all the opportunities. We don't expect that.

But in answer to your question, I don't think America has any reason not to be proud of the effort that it is sustaining in this area.

LEADERSHIP IN BIOMEDICAL KNOWLEDGE

Mr. PATTEN. With American industry, American pharmacy and American doctors, do we make our contribution?

Dr. FREDERICKSON. We are the leading nation in the world in contributing to biomedical knowledge, by a considerable margin.

Mr. PATTEN. As a result of our efforts, industry and the like, we can say we have made a fair contribution?

Dr. FREDERICKSON. I think we are making a very fair contribution. We started late and inherited a tradition from Western Europe, but since about 1945, America has accelerated its efforts and now leads the world in contributing to all these things you mention. The whole world needs to be in the act because there are many good ideas and people elsewhere, but en masse we are now the leaders in this area.

Mr. PATTEN. I saw a movie they showed about starvation and malnutrition. I had to turn it off. I couldn't take it. They were raw pictures.

Dr. FREDERICKSON. I think we have a responsibility for much of the undeveloped parts of the world that we also have to carry out, because it is a very sophisticated business.

Mr. ROYBAL. Will the gentleman yield?

Mr. PATTEN. Yes.

INFANT MORTALITY

Mr. ROYBAL. I don't believe that it is a matter of being proud or ashamed of the record at all, but are we doing enough in the field of child mortality, for example? Why shouldn't we be first instead of fourteenth. I can go down the line with various other diseases. We are a sophisticated, wealthy Nation, and I believe that we should do more in the field of health so that we will have a real good reason for being proud when we do become first. Don't you agree with that?

Dr. FREDERICKSON. I certainly agree with that. Our job certainly is not finished.

Mr. ROYBAL. Far from finished and we should definitely be doing more in this field of health. We are not now, but hope that in the future we will be able to do more so that we can take that leadership we talk about all the time.

Mr. NATCHER. Mr. Conte?

ORTHOPEDIC RESEARCH

Mr. CONTE. Last year it was indicated that you were planning an intramural orthopedic section. What has become of it?

Dr. WHEDON. An intramural unit which would engage in orthopedic research in collaboration with our arthritis and rheumatism branch has been a most desirable goal for us for some time. We have mentioned it in last year's testimony and it is also mentioned among the authorizations of the National Arthritis Act. The actual implementation of this planned unit unfortunately has not yet started for a number of reasons. From the scientific standpoint the most important factor is the need to be able to recruit, hopefully, a high-caliber scientist with all the necessary training and credentials in orthopedic surgery, whose prevailing interest is research, be it fundamental or applied, related to bones, joints and the surrounding musculature and tendons. The next consideration is to provide for such a person and his other research associates the necessary space and laboratory and clinical help—technicians and nurses—to be able to conduct productive research. The critical mass in such a new unit involves minimally about 15 positions and the necessary laboratory and clinical space for such an undertaking. I am genuinely sorry to say that in the present circumstances under which our Institute labors, such as a shrinking manpower ceiling and absolutely no possibility of obtaining new space on the campus in Bethesda and particularly in the clinical center, we have not been able to make progress in either recruiting such a person or obtaining the necessary additional manpower and space to provide a fertile environment for his and his associates' research efforts. Most importantly, under the current civil service salary ceiling, we have virtually no hope of recruiting a senior orthopedic surgeon or even an intermediate associate professor level investigator to head this unit.

Mr. CONTE. I was interested in your comments last year about use of electric current in healing of bone fractures. Can you tell us a little more about it this year?

Dr. WHEDON. This, Mr. Conte, is a research effort which now has gone on for several years. At the beginning, about 4 years ago, one of our grantees found that he could greatly aid the healing of nonhealing fractures of the bone by passing a very mild current from one portion of the fractured bone to the other through the point of fracture. To do this the earliest experiments involved placing the

electrode directly on the bone involved, that is, deep in the tissues. At that time it was shown that in many cases fractures which had shown no spontaneous healing would respond and gradually heal with the aid of this new treatment. Since that time a number of grantees have shown that such a creation of a weak electric field at the location of the nonunion between bone fragments can be induced not only by implanting an electrode directly onto the bony structures involved, but that the necessary electric field could also be induced by placing electrodes on the surface of the skin overlying the area bordering on the point of fracture. This latest development makes the procedure considerably less complicated and less risky from the standpoint of infection of the bone involved and the deep tissues surrounding it. During the last 2 years an increasing number of fractures have been studied and treated in this fashion and the results continue to be encouraging.

Mr. CONTE. In your opening statement you mentioned that the major thrust of your research would continue to revolve around the autoimmune reaction. Will you be pursuing other possibilities as well? What are they?

Dr. WHEDON. I assume, of course, that you are referring to our research related to rheumatoid arthritis. One of the major thrusts of our research will continue to revolve around the abnormal immune process which is known to underlie much of the joint destruction in this disease. For reasons which still escape us, immunologic defense mechanisms are being unleased by the body against certain constituents of the joint lining and other tissues in the body as if they were foreign substances. At the same time we recognize the possibility that an infection, possibly by a viral agent, may precede these autoimmune reactions. One could even speculate that such a hypothetical infection may affect certain tissue components and alter them chemically and physiologically and that this then triggers the autoimmune reactions which follow. We therefore intend to pursue research along the lines of possible infectious agents. In addition, of course, we will continue our research activities related to improved methods of treatment of acute attacks of the disease and improved long-term maintenance management of rheumatoid arthritis, including physical therapy and surgical methods of prophylaxis and repair.

Mr. CONTE. How much in percent will be spent this year on digestive disease as opposed to diabetes and arthritis?

Dr. WHEDON. Out of a total of approximately $180 million we estimate that this year $26 million will be spent on research related to digestive diseases and about $18 million and $14.7 million, respectively, for research related to arthritis and diabetes. Actually, Mr. Conte, these figures are misleading and do not really represent the true research effort related to any one of these diseases, What I have enumerated are dollar figures concerning research specifically related to each one of these three disease categories. In reality, however, many additional millions of dollars worth of research is conducted in more basic disciplines which underlie these diseases and which is absolutely essential if we are ever to solve the puzzles represented by them. Thus research related and important for diabetes probably must include in addition to the $14.7 million I mentioned, quite a few additional millions of dollars worth of research in endocrinology, metabolism and

nutrition which are intimately related and connected to the enigma of diabetes. The same principle holds for each of the other diseases.

NHLI OVERLAP

Mr. CONTE. How much of your effort in hematology duplicates that of the NHLI?

Dr. WHEDON. The identification of research efforts designated as "hematology" at the NIH covers a very broad spectrum. Traditionally and pragmatically, such efforts are centered in whichever Institute has, as its primary mission, the most relevance to the thrust of the research. Thus, the National Cancer Institute supports hematology research related to leukemia—cancer of the blood-forming organs; the National Heart and Lung Institute supports hematology research in problems of blood coagulation, blood banking, and certain blood diseases relevant to its basic mission; while the National Institute of Arthritis, Metabolism, and Digestive Diseases' hematology program is primarily concerned with the metabolism and basic biochemistry of blood cells—areas of immediate concern to the broad basic mission of our Institute. There is, therefore, no intent to duplicate efforts and, in fact, regular communication by NIH staff serves to coordinate effectively the NIH-wide programs in hematology, and there is no duplication to the best of our knowledge nor are there apparent opportunities for duplication to occur.

REPLACEMENT JOINT THERAPY

Mr. CONTE. How successful are replacement joints for arthritics, especially the very elderly?

Dr. WHEDON. We have had the most extensive experience with hip joints for patients whose joints have become disabled by long-standing osteoarthritis—degenerative arthritis of old age. The majority of patients who have received artificial hip joints have done well with them and have been able to walk again—in most cases with minimal aid from crutches. Most of these hip joints have functioned well for up to 10 years, but some in heavy patients or very active patients have succumbed to the wear and tear. Therefore one of the objectives of our ongoing research in this respect is to develop artificial joints which could be implanted not just in the elderly, where the required life span for the joint is probably no more than 10 to 15 years, but also in middle-aged, active persons in whom the joint has to function without mechanical breakdown for 30 to 40 years. Wearing out of artificial joints has not been a problem in other joints so far; much of this may be conditioned by the fact that the hip joint—in contrast to finger joints or elbow joints—carries a major portion of the entire body weight of the patient. There have been several types of knee joints developed in recent years and thus far they have been reported as successfully functioning in a majority of patients. Most of these joints, however, have been in operation only for 1 or 2 years.

KIDNEY RESEARCH

Mr. CONTE. On page 166 of the justification it indicates that you are phasing out 76 competing kidney research grants this year. Why is that?

Dr. WHEDON. Actually, Mr. Conte, what the notation on this page

means is that in fiscal year 1977 we have $2 million less than previously for new competing grant applications and that we will not be able to fund the equivalent of about 76 new grants related to kidney disease and urology. Our situation in this field is particularly poor and at the moment we can only fund 43 percent of all approved grantees in the area of kidney disease and urology.

INSTITUTE PRIORITIES

Mr. CONTE. What do you feel is the Institute's most important project or goal for the coming fiscal year?

Dr. WHEDON. Frankly, if this Institute were limited in its research activities to only one disease, it might be possible to give you a specific answer. Since, however, the National Institute of Arthritis, Metabolism, and Digestive Diseases is responsible for 10 different program areas including 4 of the most important chronic disease problems in the Nation; namely, diabetes, arthritis, digestive diseases, and kidney disease, I could no more single out one particular important project or goal than a mother could state unequivocally in public that of all her children she loves one particular one the most.

INTERNATIONAL EFFORTS

Mr. CONTE. Has anything of value come out of joint U.S.-U.S.S.R. collaboration with Soviet rheumatologists?

Dr. WHEDON. As you may know a number of collaborative research studies have been planned. One of these is a study, both in this country and in the U.S.S.R., concerning the efficacy of a drug called penicillamine in the treatment of rheumatoid arthritis. Similarly there will be a study concerning the effectiveness of a combination of two drugs, azathioprine and cyclophosphamide, in the treatment of the rheumatic disease, systemic lupus erythematosus. Also there will be a special joint study on juvenile rheumatoid arthritis with emphasis on the natural history of the disorder and the eventual outcome of the disease with respect to crippling deformities. Then also in a more fundamental direction, there is a program entitled "Microbiology and Immunology of Rheumatoid Arthritis and Lupus," and in that program, there will be conferences, from time to time, between American and Russian scientists, an exchange of data, and an exchange of blood samples. The exchange of such blood samples of patients has already begun. In a third area there will be joint studies and comparisons related to the surgical treatment of rheumatoid arthritis and orthopedic repair including artificial joints in crippling arthritis. As you can imagine, this program which was only started about a year and a half ago has not yet had a chance to attain its full momentum with regard to concrete research results. The early activities to date, however, have resulted in increased communication between rheumatologists from both countries, and that in itself is a desirable state of affairs.

ULCER THERAPY

Mr. CONTE. Have any further advances been made regarding the antihistamine drug for control of peptic ulcers?

Dr. WHEDON. In last year's testimony, Mr. Conte, I had mentioned the research work of Institute grantees with metiamide—a potent inhibitor of gastric acid secretion in duodenal ulcer patients. Use of this new type of antihistamine drug, however, has been associated in a

very small number of patients with a decrease in the normal number of certain white blood cells, or agranulocytosis. This depression of this type of white blood cells rectified itself once use of the drug was discontinued. Thus, because metiamide contains thiourea, which is known to produce this disorder, agents have been sought which have a similar gastric acid inhibitory action, but which are devoid of this potential toxicity. Recently a grantee of our Institute has found that another new antihistamine drug cimetidine, a recently synthesized nonthiourea antagonist to gastric acid secretion, is as effective in animal studies as metiamide, and free of significant toxicity. His studies have shown that cimetidine is markedly more effective than a widely prescribed anticholinergic drug in duodenal ulcer patients, that it does not produce acute side effects, and, thus, it may be of value in the treatment of peptic ulcer. Nevertheless, this possibility must be tested in well-controlled, long-term clinical trials to rule out any possibility of adverse side effects.

Mr. CONTE. In your professional judgment, Dr. Whedon, is this request enough to carry out the mandates given to you by Congress? If not, which areas need more work?

Dr. WHEDON. As I mentioned earlier, Mr. Conte, this budget does not include the recommendations of the National Diabetes Commission which were made in December 1975. The Commission's report makes specific budgetary recommendations, and I endorse these, particularly with respect to the research and training areas. Here the recommendation was for an increase of over $13 million, most of it directly in diabetes and parts of it in diabetes-related endocrinology, metabolism, and nutrition. In addition, the Commission recommended institution of a program of multipurpose centers with a first year addition of funds amounting to $8 million.

Although the National Arthritis Commission has not yet finished its report I am certain that this Commission will recommend funding for the new programs in arthritis authorized in the National Arthritis Act—specifically for comprehensive (multipurpose) centers and for an arthritis data bank. In addition, I expect the Commission to make recommendations concerniing an increase in research and research training in the area of arthritis.

Besides these new programs mandated by congressional legislation, there are several other areas, in which the two subcommittees on appropriations have expressed concern, which need an increased level of effort such as digestive diseases, kidney disease, bone and skin diseases, and nutrition. Also in order to carry out the additional level of effort in research, additional support for research training is needed through the mechanisms available to us.

To carry out the recommendations of the appropriations committees of recent years and to carry out the broad new mandates given to this Institute by the Congress in the new national diabetes and arthritis legislation, the Institute is in strong need of additional manpower. The combination of a shrinking manpower ceiling for this Institute and our expanded activities of recent years have brought us to the point where no additional activities can be carried out unless our manpower ceiling is significantly increased.

Mr. NATCHER. The subcommittee will insert at this point several reports prepared by Dr. Whedon and his staff, and also the justifications of the budget.

ARTHRITIS, RHEUMATIC DISEASES, AND RELATED DISORDERS

Arthritis, rheumatic diseases, and related disorders represent a grave public health problem, afflicting more than 18 million people in the United States with pain and severe crippling, at a cost of about $4 billion to the nation annually. The most severely crippling form of these disorders, rheumatoid arthritis, afflicts about 5 million Americans. The most prevalent form of arthritis, known as osteoarthritis, affects more than half of all people between the ages of 55 and 64, who show evidence of this degenerative joint disease. Important advances are being made against these diseases, however, as a result of extensive biomedical investigations at both basic and applied levels conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Allergy and Infectious Diseases.

Obligations for Programs in Arthritis

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism & Digestive Diseases					
Arthritis	$13,808,000	$14,076,000	$16,860,000	$18,095,000	$17,750,000
National Institute of Allergy and Infectious Diseases					
Arthritis	$7,858,898	$8,529,237	$8,970,249	$11,650,000	$13,400,000
Total	$21,666,898	22,,605,237	$25,830,249	$29,745,000	$31,150,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Arthritis, including numerous disorders of the joints characterized by inflammation and eventual degenerative changes, is man's oldest known chronic illness. Arthritis refers to the diseases which attack the joints. Other types, such as those that involve the muscles, tendons, ligaments, or bursae, are referred to as rheumatism. The effects of rheumatic disease may vary from a slight pain, stiffness or swelling to crippling and total disability.

The terms "arthritis" and "rheumatism" encompass about 100 different disorders, of which more than a dozen represent serious public health problems. These include rheumatoid arthritis, degenerative joint disease, also called osteoarthritis, connective tissue disorders such as systemic lupus erythematosus, and arthritis associated with metabolic abnormalities such as gout.

Each year the rheumatic diseases cause time lost from work equivalent to the work of half-a-million people. The cost of disability payments by the government to individuals crippled by arthritis during this decade will amount to more than a billion dollars.

The emphasis of much research is necessarily on improving treatment of these diseases and on developing new procedures and materials, such as those which have made the total replacement of hips and other joints possible. In the long run, even more substantial progress can result from work in the fundamental disciplines which underlie our understanding of arthritis. Investigators and grantees of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) are developing basic information which should serve to explain problems of arthritic inflammation and tissue destruction and to clarify the immunologic mechanisms apparently involved in some of these processes -- thereby making possible better and more effective treatment.

Arthritis became the focus of an intensified national effort in 1975 with the signing of the National Arthritis Act by the President of the United States. This legislation calls for a broadening of arthritis-related activities, including preparation of a National Arthritis Plan.

In response to this Congressional mandate, the National Commission on Arthritis and Related Musculoskeletal Diseases is preparing a long-range plan which will delineate major initiatives in the effort to control arthritis and related disorders. The Commission, under the chairmanship of Dr. Ephraim P. Engleman of the University of California at San Francisco, has drawn advice from the medical profession, both research and practicing physicians, directors of the concerned Institutes of the National Institutes of Health, and representatives of the general public and the voluntary health agencies most vitally concerned with rheumatic and musculoskeletal diseases. The Commission is expected to complete the preparation of its report as a long-range plan in April 1976.

The NIAMDD will perform a central role in this concerted effort against these grave disorders and will fulfill all the requirements of the National Arthritis Plan insofar as its fiscal and manpower resources will permit.

RHEUMATOID ARTHRITIS

Research scientists are continuing their efforts to discover the cause(s) of rheumatoid arthritis. This disease often leads to severe disability and no permanent cure has yet been found. Researchers have sometimes found certain infectious agents in close association with tissues inflamed by rheumatoid arthritis, but none of these organisms has been found to be a cause of the disease. Many investigators believe that the mechanism which causes the widespread chronic inflammation affecting various systems of the body is an abnormal reaction of the body's immune system. Such a reaction may be stimulated by infection and may result in a misdirected attack by the body's defense systems on its own tissue (an autoimmune reaction).

Research on the Mechanisms of Immunity

Studies have demonstrated an approximate correlation between the severity of rheumatoid arthritis and the presence of rheumatoid factor in the blood. This factor is lacking in some patients with rheumatoid arthritis, a situation which can make diagnosis and classification more difficult. Studies in recent years have shown the value of utilizing what is known about the complement

system, a major link in the body's immunological responses, in evaluating rheumatoid arthritis patients who are serologically negative for rheumatoid factor. This evaluation is accomplished through the determination of complement levels in fluid recovered from inflamed joints.

About two years ago, Dr. Frederic C. McDuffie and his associates at the Mayo Clinic, Rochester, Minnesota, identified four distinct 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.

Dr. Nathan J. Zvaifler, an Institute grantee at the University of California, San Diego, 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 suggests that antigen-antibody complexes are responsible for activation of the complement sequence, followed by joint tissue damage.

In work with Dr. Norman Talal, at the VA Hospital associated with the University of California, Dr. Zvaifler and his associates have detected elevated concentrations of the protein beta$_2$-microglobulin in the saliva and synovial fluid, respectively, of patients with Sjogren's syndrome and rheumatoid arthritis. The low molecular weight protein is present in low concentration in normal serum and urine; but is increased in the serum and urine of patients with renal tubular disorders and in kidney transplant recipients, particularly during rejection crises (when the body is mobilizing its immune defenses against the "foreign" graft). Although its exact function is unknown, beta$_2$m is believed to play a role in immunologic reactions since it is part of the HL-A antigen complex on the lymphocyte cell surface. The researchers (both former staff members of NIAMDD's intramural research Arthritis and Rheumatism Branch) suggest that measurement of concentrations of this protein in inflammatory fluids may offer a simple method of quantifying local disease activity and in monitoring treatment in pathological autoimmune states. The investigators suspect that such increased concentrations result from local production of beta$_2$m by lymphocytic and inflammatory cells which infiltrate target tissue sites in autoimmune diseases such as Sjogren's syndrome and rheumatoid arthritis.

Another Institute grantee, Dr. Morris Ziff of the University of Texas Southwestern Medical School, after studying cells known as B-

lymphocytes under the electron microscope, has found that immune responses in inflamed joints of individuals with rheumatoid arthritis 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 investigators and grantees continue to search for viral agents associated with this disease, and have tested cells taken from rheumatoid patients for the presence of numerous viruses, but so far no evidence of a viral trigger has been found.

Treatment of Rheumatoid Arthritis

Treatment of rheumatoid arthritis varies widely, but in the early stages the therapy program is concentrated on relief of pain, control of inflammation and prevention of deformity. A major share of current research is aimed at controlling this disease by varieties of new and old drugs, sometimes in combination. One of the newest studies focuses on treatment with the drug penicillamine. The use of immunosuppressive drugs is also being investigated intensively, not only in treatment of rheumatoid arthritis, but also in cases of systemic lupus erythematosus, which affects some 50 thousand new patients each year.

A recent study conducted by Dr. Charley J. Smyth and associates at the University of Colorado indicates that low dose cyclophosphamide plus prednisone is effective in suppressing disease activity in patients with rheumatoid arthritis (RA). The treatment of severe RA with high doses of cyclophosphamide alone is beneficial, but is associated with an increased incidence of adverse side reactions, while low doses of the cytotoxic agent are often of little benefit.

The investigators found that patients under low dose cyclophosphamide plus prednisone therapy showed progressive decreases in joint inflammation and improvement of joint function with fewer immediate toxic reactions than in patients given cyclophosphamide alone. The researchers report, however, that further study is needed to determine the long-term, serious side-effects of the combination therapy as well as whether the relatively low toxicity of this treatment results from the lower doses of cyclophosphamide or from the concomitant use of prednisone.

Previous research by Dr. Morris Ziff and Dr. Eric R. Hurd at the University of Texas Southwestern Medical School had demonstrated the efficacy of cyclophosphamide in treatment of RA. These investigators are continuing to investigate the mechanism of action involved. They have found that patient improvement is correlated with reduction in the numbers of monocytes and small-lymphocytes in the blood, an observation which provides a means of monitoring treatment and might offer a clue to the mechanism of action of the drug.

Other drugs under study with Institute support include methotrexate, nitrogen mustard and chlorambucil, all of which seem promising in certain cases, but they too present problems of side effects. Use of nitrogen mustard is limited by the fact that it must be injected and by its toxicity. The work of Dr. John T. Sharp and associates at the Baylor

College of Medicine has shown encouraging results of gold therapy, with the arrest of bone and cartilage destruction (a slowing of the rate of joint damage) in several patients.

Another approach to treatment currently being examined is more specific control of the inflammatory process. Researchers have found that collagen breakdown (collagen is the basic structural protein in connective tissues of the body, including joints) is four times greater than normal at the elevated temperatures found in knee joints afflicted with rheumatoid arthritis. This knowledge has suggested a new rationale for suppression of joint inflammation based on decreasing internal joint temperatures. Related research is contributing more solid evidence of the role of collagenase (a collagen-digesting enzyme) in the process of joint inflammation.

Surgeons at the NIH Clinical Center in Bethesda, Maryland, are continuing their research with synovectomy or surgical removal of the thickening synovial tissue of the diseased joints of RA. These studies continue to confirm some efficacy of this approach in reducing inflammation and improving joint function. Future research will be needed to determine which patients can be helped with synovectomy and what the long-term effects of the surgery will be.

Juvenile Rheumatoid Arthritis

There are distinctions between rheumatoid arthritis in adults and the various subgroups of rheumatic disease known as juvenile rheumatoid arthritis (JRA), which affect those under 16 years old. In addition to the severe joint pain, stiffness, and crippling found in adult rheumatoid arthritis, JRA also causes growth disturbances and is responsible for more frequent occurence of high fever and skin rash than is found among older patients. Because of these distinctions and others -- such as systemic and visceral disorders, and frequent absence of rheumatoid factor in the blood -- JRA is considered a separate clinical entity among rheumatic disorders.

Studies have linked an increased frequency of the histocompatibility antigen W27 with ankylosing spondylitis associated with chronic inflammatory bowel disease, Reiter's disease, and acute anterior uveitis. Although investigators were unable to link increased W27 frequency with JRA in a study of 50 patients in 1973, subsequent studies seemed to indicate such a link, suggesting that all of the aforementioned disorders may have a common etiology.

In a recent research project, Institute grantee Dr. Peter H. Schur and associates at the Robert B. Brigham Hospital, Boston, sought to clarify this discrepancy and to establish whether there is such a link by conducting a long-term study of 123 patients with JRA. Their observations fail to support the contention of others that W27 is found more frequently than expected in patients with JRA. The investigators suggest that if there is a genetic factor involved in the cause of JRA, as suggested by other researchers, it does not appear to be associated with any of the inherited HLA markers, including W27, studied to date.

OTHER CONNECTIVE TISSUE DISORDERS

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a connective tissue disorder which affects some 50,000 new victims each year. This chronic inflammatory

disease can affect the joints and several organs such as lung, spleen, heart or kidney. The evidence suggests that SLE may be a disorder of the immune system of the body, triggered, perhaps, by an infectious process (in some cases it is known to be caused by sensitization to certain drugs). NIAMDD researchers at the NIH Clinical Center, however, suggest that numerous directions of study may be useful in tracking down the causes of this disease, including investigation of genetic, viral and immunologic factors. The Institute scientists also believe it is important to continue the search for chemotherapeutic approaches to controlling SLE, and they are continuing to explore the value of the immunosuppressive drugs cyclophosphamide and azathioprine in treating complications of this disease.

Recent studies have shown that the estimated five-year survival for all patients with SLE improved from around 40% in 1966 to around 60% in 1975. In the subgroup of SLE patients with the grave kidney complication, diffuse proliferative glomerulonephritis (DPG), however, five-year survival estimates have ranged only from 20% to 25% following onset of SLE.

NIAMDD grantee Dr. Ronald P. Messner and associates at the University of New Mexico Center for the Health Sciences have conducted a study showing a close correlation between abnormal changes in brain scans and neurologic evidence of central nervous system lupus erythematosus. These researchers say that the brain scan may be a rapid and sensitive tool that can be used to diagnose cerebral lupus erythematosus, since it appears capable of detecting the permanent vascular damage that may occur as well as transient lesions that may represent vasculitis. They say that more research is needed to correlate the brain scan technique with other markers of lupus cerebritis, such as spinal fluid complement levels and serum immunoglobulin levels.

Lupus Nephritis

There is no satisfactory therapy for lupus nephritis, a grave kidney disorder associated with systemic lupus erythematosus. In 1971, Dr. Alfred D. Steinberg and Dr. John L. Decker of the Institute's Arthritis and Rheumatism Branch showed that the cytotoxic and immunosuppressive drug cyclophosphamide is superior to placebo in the short-term treatment of lupus nephritis. In a recent study they have compared the relative efficacy of two such drugs, cyclophosphamide and azathioprine, and placebo in the treatment of such patients.

Cyclophosphamide was found to be significantly superior to both azathioprine and placebo in the treatment of lupus nephritis, while azathioprine was not significantly better than placebo in any individual measure. Although cyclophosphamide led to somewhat greater improvement than did azathioprine, additional long-term data will be required to establish the role of these potent immunosuppressive drugs in the routine management of lupus nephritis.

Although the mechanism of action of cyclophosphamide and other immunosuppressive drugs in the treatment of lupus nephritis is as yet unknown, there is considerable evidence to indicate that cyclophosphamide and prednisone, in particular, act synergistically (or to reinforce each other). Ongoing long-term studies of patients at the Clinical Center, the NIAMDD researchers say, may provide more insight into the mechanisms of action and the efficacy of these drugs.

Psoriatic Arthritis

As already mentioned, investigators have documented the remarkable association of the histocompatibility antigen W27 with ankylosing spondylitis, Reiter's syndrome, and the spondylitis associated with inflammatory bowel disease. Recently Institute grantee Dr. Paul I. Terasaki and associates at the University of California, Los Angeles, extended these observations to include still another "rheumatoid variant" disorder -- psoriatic arthritis. The New findings indicate that the frequency of the inherited tissue type marker W27 is significantly increased in patients with psoriatic arthritis complicated by spondylitis, but not in psoriatic patients with peripheral arthritis alone. These observations, coupled with previous findings, strongly suggest some common inherited susceptibility operative in specific rheumatoid-variant rheumatic diseases. The researchers say that positive W27 findings in males with psoriatic arthritis may predict their enhanced risk of developing spondylitis. Further study of W27 frequency in the rheumatoid variant disorders should provide a better explanation of the interrelationships and familial aggregation known to exist in these conditions.

Septic Arthritis

Successful treatment of patients with acute infectious arthritis requires appropriate antimicrobial therapy and removal of purulent material from the joint. Classically, such drainage has been accomplished surgically, although needle aspiration has proved effective in recent years. Controversy currently exists concerning which mode of drainage should be employed initially. NIAMDD grantee Dr. Alan S. Cohen and his associates at Boston University have evaluated both procedures as initial modes of drainage in a recent study of 59 patients with acute septic arthritis. While full recovery was noted in 42% of patients treated surgically at the outset, 67% of those treated by needle aspiration recovered completely.
Thus, it would appear that needle aspiration is preferable as the initial mode of drainage, except in cases of hip infection, which requires surgical drainage. In reporting their findings to rheumatologists, the researchers say that the study points up the necessity of instituting therapy immediately following diagnosis of septic arthritis, inasmuch as recovery was complete in less than a third of the patients studied who had shown symptoms of infection for more than a week prior to initiation of therapy.

Osteoarthritis

Degenerative joint disease, commonly known as osteoarthritis, appears to be, in part, a phenomenon of the aging process but has also been clearly related to unusual wear on cartilage, the resilient, glistening white material which covers the ends of bones at the joints. The wear is thought to occur through small, repeated, damaging injuries, or "microtrauma," over extended years of use; cartilage damage may develop in accelerated form if unusual weight has been supported, as in obesity, or if the weight bearing surfaces are even slightly out of line due, for example, to fractures suffered in youth. That more generalized, systemic factors are also involved is clear from familial cases suggesting heritable features and from the early appearance of the condition in certain metabolic (or biochemical) states known to affect the composition of cartilage.

The most disabling form of degenerative joint disease involves the hip joint where the disease may produce constant pain and extreme limitation of motion reducing the sufferer to bed and wheelchair existence. It is this condition, degenerative joint disease of the hip, which has responded most dramatically to joint replacement as described under "Orthopedics."

New information on the precise biochemical composition of cartilage, as well as the sequence of events in its destruction in osteoarthritis, is now increasing our understanding of the process and revealing possibilities for preventing the deterioration. The struts of cartilage are composed of the tough, relatively rigid protein called collagen. The matrix interspersed among these structures is composed of enormous sugar compounds called proteoglycans which hold in their interstices, or crevices, large amounts of water. These three elements, collagen, proteoglycans, and water, give cartilage its resilient, shock absorbing, and smooth gliding properties so vital to normal function. Chemical and structural alterations of both collagen and proteoglycan occur with aging and are most pronounced in cartilage samples taken from those joint areas which show the most osteoarthritic change.

The collagen and the proteoglycan of cartilage are manufactured and maintained by special cells within the tissue, the chondrocytes. As the cartilage suffers wear and breaks down, these cells appear to respond with abortive attempts at repair. The chondrocytes, turned on, produce new collagen and proteoglycan and thus new cartilage. Unfortunately, this new cartilage is not very well placed anatomically and seems to have much less strength and durability than the original tissue.

Recent work by Institute-supported investigators, Dr. Klaus Kuettner and associates at Rush Medical School in Chicago, and Dr. David Howell and associates at the University of Miami, has focused on the initial deterioration in osteoarthritis. They have shown that the chondrocytes, in addition to their potential for inadequate repair (as described above), also contain destructive or lytic enzymes which, upon release from the cell, play a destructive role. Unusual levels of these injurious enzymes have been found in the matrix of cartilage in the early stages of osteoarthritis.

Dr. Howell believes that it is possible to inhibit these destructive enzymes chemically, thus blocking the breakdown of the tissue. It may also be possible to restore chemically the chondrocytes' normal repair function. The investigators emphasize that future work requires close collaboration between biochemists and bioengineers because of the close relationships between the biochemical events and the mechanical properties of the tissue. When these relationships in cartilage are fully understood, the prevention of degenerative joint disease will be a real possibility.

BONE DISEASES AND ORTHOPEDIC RESEARCH

Development of specific artificial joints, such as shoulder, elbow, finger, hip and knee joints, and methods for attachment of these to bones, tendons or muscles are major interests of NIAMDD orthopedics investigators.

Intensive interest in recent years in development of better implantable materials has brought an influx of engineers and polymer and ceramic chemists into biomedical research. Current studies aim at finding 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 its skeletal or muscular environment and will not necessitate replacement throughout the lifetime of the patient. Successful transplantation of artificial joints depends upon a better understanding of the graft-rejection process and thus fundamental immunology, bone metabolism, fracture healing, skeletal attachment, skeletal-soft tissue trauma, and other factors in the healing process. Research in all of these areas

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continues. Efforts which involve connective tissues and cartilage are directed toward a better understanding of biochemical reactions, gross and cellular anatomy, genetic factors, and enzymology of these tissues, as well as of the process of tissue-skeletal repair.

Total Hip Replacement

The most advanced artificial joint under study is undoubtedly the artificial hip. Hip joint replacement is one of the most successful orthopedic procedures in restoring mobility to the patient, even in cases where reconstructive surgery has failed. Investigators are currently working with a variety of reinforced plastics, ceramics and metals in an ongoing effort to improve the effectiveness and durability of hip replacement. 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. The outlook for replacement of joints of all kinds in the treatment of arthritic conditions is rapidly improving, and the Institute will continue to support research evaluating total hip replacement and related work at centers throughout the United States.

Bone Research

In recent years a number of NIAMDD grantees have described some improvement in bone fracture healing in response to electrical stimulation by electrodes implanted within the bone near the fracture site. Such patients suffered from either a long-term non-healing fracture, or from a congenital pseudarthrosis ("false joint") that was refractory to pinning, grafting or fusion.

Now Institute grantee Dr. C. Andrew Bassett of the Columbia College of Physicians and Surgeons has successfully promoted regeneration and fusion of bone in five children with congenital pseudarthrosis, utilizing an electromagnetic technique that requires no electrode implantation or large voltage. Good union of the fracture, with no recurrence of the disease, was observed in all five patients, with the first patient having been followed for as long as 18 months. The new technique involves low-frequency, low-intensity electromagnetic fields induced in the involved tissues by application of electrodes to overlying skin. Although the mechanism of action is still unclear, healing is believed to involve a complexing of cations such as calcium and potassium, and their release from binding sites following electromagnetic radiation. Dr. Bassett suggests that his technique might ultimately be applicable to routine fractures and may cut healing time by as much as 50 percent.

The National Institute of Allergy and Infectious Diseases Research Effort in Arthritis, Rheumatic Disease, and Related Disorders

The National Institute of Allergy and Infectious Diseases (NIAID), because of its traditional concern with microorganisms and the development of immunity to them, supports substantial research complementary and relevant to NIAMDD-supported studies on arthritis, especially rheumatoid arthritis, rheumatic disease, and related disorders.

NIAID research in this area is rooted in the basic scientific discipline of immunology. Many investigators now believe that the inflammatory reaction characteristic of arthritis is due to an abnormal response of the body's immune system, initiated either by infection or by a misdirected attack on

an individual's own tissues.

Most recently, investigators have recognized that inherited factors are also involved. NIAID's long-term support of research on techniques for matching organ transplants and recipients is now paying off in terms of new immunochemical tools which can also be used to explore the relationship of inherited tissue antigens and susceptibility to disease.

In this report, examples of NIAID-supported research activities are described under the headings of causation, pathologic mechanisms, therapy, and genetics of arthritis, rheumatic disease, and related disorders.

Causation

The arthritis-related diseases embrace a number of disorders which have been identified with considerable certainty as being immunologically-mediated inflammatory diseases. Some, such as rheumatoid arthritis and systemic lupus erythematosus, have revealed immune complexes and sensitized lymphoid cells which indicate that a specific antigen, perhaps that of an infectious agent, has initiated the disease. Although studies of animal models lead to the suspicion of a microorganism as the causative factor in rheumatoid arthritis, the classic pattern of an infectious disease has not been detected in epidemiologic studies. Nevertheless, because organisms have been recovered from synovial (joint) fluid and tissue, the NIAID has supported various studies seeking to clarify the etiology of these disorders.

Among these studies are those by Dr. Harry E. Morton at the University of Pennsylvania who has been investigating the involvement of the microorganisms known as mycoplasma in some types of rheumatoid-like arthritis. He and Dr. Lewis Thomas, Sloan-Kettering Institute for Cancer Research, have independently developed serologic test systems for detection of mycoplasmal and other microbial antigens in synovial fluids of affected joints. In a similar manner, Dr. Johannes Storz, Colorado State University, has been conducting studies of chlamydial infections as a cause of poly-arthritis and chronic infections of synovial tissues in experimental animals.

A research group at the University of Tennessee, supported in part by an NIAID grant to Dr. Gene H. Stollerman, has provided electron microscopic evidence for the direct infection of joint tissue by the bacterium, Neisseria gonorrhoeae, in a patient exhibiting the early inflammatory symptoms of arthritis. This observation suggests that the early inflammatory response may be initiated by the infecting microorganism rather than as a consequence of hypersensitive reactivity to microbial antigens.

Like rheumatoid arthritis, the causes of systemic lupus erythematosus (SLE) are unknown. Viruses, especially the persistent slow-growing types, have been suggested but none has been isolated consistently from patients. The bulk of the evidence implicating viruses is provided from studies of analogous infections in experimental animals.

A large amount of this information has been obtained from studies of lupus-like infection which develops spontaneously in the New Zealand strain of mice. These genetic hybrids produce unusually large amounts of antibody against DNA, a component of cellular nuclear material, and against oncornaviruses with which these animals are naturally infected. Complexes of these antigens and antibodies are formed in the circulation and, on their deposition in tissue, form lesions which are believed to be responsible for the pathologic process.

A research group, headed by Dr. Robert A. Schwartz, at the New England Medical Center has developed and is studying a canine model of systemic lupus erythematosus. Their colony of inbred dogs exhibit the classical symptoms of this disorder and produce anti-nuclear antibodies. The disease can be transmitted to newborn dogs and mice with materials prepared from affected animals. The investigators have evidence that a oncornavirus-like agent may be involved in the initiation and transmission of this disease, too. Information being obtained from the canine model appears complementary to that developed in the New Zealand strain of mice and may confirm the key roles played by genetic and immunologic factors in systemic lupus erythematosus.

A sensitive fractionation procedure for nuclear materials, developed by NIAID grantee Dr. Vincent Agnello at Tufts University, now permits quantitative studies of reacting blood substances. Use of this procedure is expected to help define their relative roles in the development of SLE.

Dr. Hugh O. McDevitt at Stanford University is also studying auto-antibody patterns in SLE and has offered substantial leads to the causes and genetics of this condition. His work on patient populations, is relating clinical laboratory findings in lupus nephritis with prognosis and response to therapy. For example, he has shown that the emergence of nephritis does not necessarily depend upon the autoantibody formation *per se* but upon other biologically reactive and genetic factors under study.

Pathologic Mechanisms

The affected joint of an arthritis patient is characterized by: (a) the presence of large numbers of white cells known as polymorphonuclear leukocytes in the synovial fluid; (b) an accumulation of other cells in the deeper layers of the synovial membranes; (c) thickening of this membrane; and (d) injury to joint tissues by destructive enzymes released from the inflamed synovial membrane. These processes account for the heat, pain, and swelling of the affected joints in arthritis and, collectively, lead to destruction of joint cartilage, erosion of adjacent bone, and the subsequent loss of joint function.

Current evidence indicates that, in rheumatoid arthritis, immunological events play a major role in initiating and maintaining the damaging sequence of events. Many studies of patients with active disease have supported the concept that antigen-antibody complexes are central to the pathologic process in that they are responsible for the activation of complement, the formation of chemotactic factors, the subsequent migration of "scavenger" cells, and the release of tissue destructive enzymes from these cells into the synovial tissue and fluid.

Immune complexes contain rheumatoid factors, which are antibodies that may belong to any of the major classes of immunoglobulins (IgG, IgM, IgA).

It now is clearly important to define the possible role of cell-mediated immune responses in arthritis since both thymus-dependent (T) and bone-marrow (B) lymphocytes have been found in synovial tissues, as well as the chemical mediators of cellular immunity, such as migration inhibitory factor, blastogenic factor, and lymphotoxin.

The development of SLE also is associated with unusual and exaggerated immune responses. These give rise to antibodies that are capable of reacting

with tissue components of the host, and with some microbial antigens. Antibodies may be specific for single or double-stranded DNA, for viral and synthetic RNA, or for DNA:RNA hybrids. Antibodies to native-DNA and to nucleoprotein have a high frequency in SLE patients, but antibodies to denatured DNA are present in many other disorders.

An affected individual's immune response to this nuclear antigenic material may be modified, according to work carried out by Dr. Yves R. Borel at Tufts University in appropriate animal models. His studies have helped show that induction of tolerance may be beneficial and that while cortisone derivatives can reduce the inflammation in SLE patients and improve symptoms, these drugs may paradoxically and adversely prevent the induction of a tolerant state, unless dosage factors are taken into consideration.

Kidney problems in SLE result from the deposition of immune complexes in the glomerulus -- the filterbed of the kidney. DNA, anti-DNA, and other antigen-antibody complexes have been detected on the glomerular membrane. In patients with active SLE, circulating immune complexes are detectable and complement components are consumed due to activation by immune complexes. One of the most common and perhaps clinically the most significant targets of such circulating complexes is the kidney. Once deposited, these immune complexes produce local inflammation and serious damage to both glomerular structure and function.

The initiation and maintenance of the inflammatory response appears to be the central pathological mechanism involved in rheumatoid arthritis and related disorders. The NIAID supports much research on the molecular and cellular events involved in the inflammatory process. For example, Dr. Frank J. Dixon, Scripps Clinic and Research Foundation, is directing a NIAID program project on the injurious nature of immune complexes. Also receiving support for continuing investigations of antibodies involved in immune complexes is Dr. Henry G. Kunkel, Rockfeller University, one of the early workers involved in the discovery of rheumatoid factor.

Contributions of these two NIAID grantees to the development of contemporary concepts of the immunopathology of rheumatoid arthritis and related disorders received national recognition recently when Dr. Dixon and Dr. Kunkel were named co-winners of the Lasker basic medical research award for 1975. Both scientists were recognized as being primarily responsible for establishing the scientific discipline of immunopathology -- the study of the harmful effects of the immune response -- while they pursued their research on immune complex diseases.

Studies of complement and other chemical mediators of the inflammatory process represent another major segment of research relevant to arthritis and related diseases. Work currently supported by NIAID ranges from studies of the chemical structure of complement, its activation processes and component functions, to the chemistry and release of kinins or other mediator substances associated with immediate hypersensitivity reactions. Projects directed by Dr. Peter A. Ward, University of Connecticut, and Dr. K. Frank Austen, Robert B. Brigham Hospital, are centered in this area as are studies by Dr. Allen Kaplan and his co-workers in NIAID's Laboratory of Clinical Investigation.

Another thrust of NIAID-supported research activity centers on the participation of cells and their constituents in the inflammatory process. Attention in this area has been focused on the soluble lymphocyte factors which attract and maintain scavenger cells at the inflammatory site, the

processes leading to biochemical activities of macrophages, and the enzymatic capabilities of activated macrophages. Drs. Peter A. Ward and Stanley Cohen, University of Connecticut, are investigating the chemical stimuli which attract scavenger cells to inflammatory sites while studies of the functions of these cells are being conducted by a number of investigators.

Therapy

Because the causes of rheumatoid arthritis and related disorders are still unknown and their disease processes are not yet fully understood, current treatment is directed primarily at suppression of inflammation and the associated immunologic events. The NIAID has long had a special interest in use of anti-inflammatory and immunosuppressive therapy in organ transplant patients, and, thus, has provided support for research which has also had relevance to the treatment of arthritis and other inflammatory diseases.

Acetylsalicylic acid (aspirin) is by far the most commonly used anti-inflammatory drug; its efficacy and safety in decreasing inflammation have been well documented. However, some patients cannot take large doses of aspirin because of toxic gastrointestinal irritation and others are allergic to this drug. To avoid such side-effects, physicians have prescribed derivatives of salicylic acid but none has yielded higher therapeutic efficacy.

Small and limited controlled trials of the immunosuppressive drugs -- cyclophosphamide and azathioprine -- have demonstrated marked suppression of inflammation. However, drugs of this category induce an indiscriminate suppression of the immune response. Hence, a very potent drug of this type renders a patient incapable of an immune response and thereby subject to serious and life-threatening infections.

It is not certain how immunosuppressive drugs work. They induce a slow depletion of pools of certain cells such as macrophages and lymphocytes. Preparations known as anti-lymphocyte sera would conceivably achieve the same result but they have not been used clinically to any significant extent except in transplant recipients. The influence of anti-lymphocyte sera on immunologic responsiveness is being examined however by such NIAID grantees as Drs. A.P. Monaco, Harvard University, and R.F. Barth, University of Kansas.

Genetics

Recently it has become apparent that genetic factors play a major role in predisposition to some of the inflammatory rheumatic diseases. Principal findings have been concerned with the demonstration of an extraordinarily strong association between certain histocompatibility (HLA) antigen types and certain rheumatic disease syndromes. Histocompatibility antigens are inherited substances found on an individual's white cells which help determine the acceptance or rejection of an organ transplant. In general, the closer the match between histocompatibility antigens of an organ donor and recipient, the better the chances for graft survival.

These findings in regard to HLA antigens have been superimposed upon a larger body of pre-existing epidemiologic and family study data which indicated an increased familial incidence of several rheumatic diseases, thus suggesting that genetic as well as environmental factors play a major role.

In man, the major histocompatibility complex contains two types of genes which determine transplantation antigens. One group of genes determines the classical, serologically defined (SD), transplantation antigens which are found on all tissues of the body. The other group consists of genes which determine the mixed leukocyte culture reaction and the leukocyte defined (LD) antigens.

NIAID is a major source of the HLA antisera used for genetic and transplantation studies. These antisera are available as testing agents to investigators upon request.

The most striking association between HLA genes and disease entities has emerged from studies of the SD antigen W27 and ankylosing spondylitis. However, since documented cases and family studies have indicated that ankylosing spondylitis can occur in the absence of W27, it is believed that other genes may also be involved in predisposition to rheumatic disorders.

Recent evidence indicates a weak association between rheumatoid arthritis and SD antigen, W10 as well as LD antigen, Ra.

Although studies of SLE have not yielded consistent association with the presence of specific SD antigens, the increased prevalence of this disease and the presence of anti-nuclear antibodies in first-degree relatives of SLE patients indicates that a genetic control mechanism may well be involved. It is anticipated that, as newer knowledge is gained and technological advances occur, more definitive approaches for probing genetic influences on the immune response system and disease susceptibility will be developed.

Although the NIAID interest in immunogenetics logically developed from its involvement in organ transplantation immunology, it has been broadened to explore the problem of genetic regulation of immunity to infectious, allergic, and immunologic diseases.

A major technical advance in the study of these gentic controls has been reported recently by an NIAID-supported research group at the University of Wisconsin. Dr. Fritz H. Bach and his associates have developed a rapid procedure to identify the LD antigens by modifying the mixed leukocyte culture reaction. Their new test employs "primed" blood lymphocytes and offers the potential for developing and storing for reference, typed lymphocytes to be used in characterizing an individual's LD antigen profile in much the same way the SD antigens have been typed. The application of this test system to the rheumatic diseases may clarify the genetic mechanisms influencing susceptibility and resistance to these disorders.

OUTLOOK

Looking to the future of research in this field, we must pursue numerous areas of investigation to improve knowledge in the various approaches to treatment, to expand on the gains that have been made in the field of immunology, to continue the search for a possible infectious agent in rheumatoid arthritis, and to improve upon our still meager insights into the underlying pathophysiologic mechanisms of these disorders. The examples of research in arthritis presented in this report are but a few of more than 150 ongoing, Institute grant-aided or NIH Clinical Center studies covering the range of rheumatic diseases. A comprehensive program of research, education, prevention, and rehabilitation through multi-disciplinary studies focusing on the central problems of these diseases will become scientifically expedient as the recent advances in virology, immunology, and epidemiology begin to bear fruit. This continuing effort is improving our understanding, treatment and control of these disorders, and is increasing the fund of basic knowledge from whence the eventual cures and methods of prevention will come.

COOLEY'S ANEMIA

Providing insight into the genetic basis of inherited blood disorders such as Cooley's anemia requires a thorough study of the processes and functions of blood cells and the blood forming organs. Estimates indicate 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 of which many are of genetic origin.

At least 2,400 patients with Cooley's anemia are being maintained in this country with the aid of chronic transfusion therapy. The problem is of greater scope elsewhere in the world, the thalassemias being the most common inherited single gene defect. 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	1976 Estimate	1977 Estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, & Digestive Diseases:					
Cooley's anemia.....	$1,007,000	$1,105,000	$1,211,000	$1,239,000	$1,187,000
National Heart and Lung Institute:					
Cooley's anemia.....	1,900,000	2,262,000	2,569,000	3,000,000	3,000,000
Total.....	2,907,000	3,367,000	3,780,000	4,239,000	4,187,000

National Institutes of Health
National Institute of Arthritis, Metabolism, and Digestive Diseases

Much of our knowledge of Cooley's anemia, (also known as Thalassemia Major, Mediterranean anemia, Hereditary Leptocytosis, and Familial Microcytic Anemia) has been acquired during the last 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. Research supported and conducted by NIH has contributed much to the knowledge of the molecular structure of hemoglobin, the key substance in red blood cells which carries oxygen from lungs to tissues, and of the different sequence of amino acid building blocks in abnormal hemoglobins.

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) is investigating many blood disorders, including Cooley's anemia, either through research in its Bethesda, Md., laboratories and clinics, and/or through numerous grants to scientists at research centers across the country. The National Heart and Lung Institute (NHLI) shares the responsibility for Cooley's anemia research with NIAMDD. This past year investigators supported by these two Institutes have contributed several significant research findings.

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. It is characterized by the production of abnormally thin red blood cells with abnormal mechanical fragility and by a severe anemia which appears soon after birth. Serious effects include enlargement of the spleen and liver and hyperactive bone marrow that may produce thickening of facial bones. The anemia is due to the inability of the bone marrow to synthesize the complete hemoglobin protein that is normally contained in the red blood cells. 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.

As in many genetic blood disorders, those who inherit the disease trait from only one parent are "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.

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 the frequent therapeutic transfusions. Carriers are generally healthy and live an average life span although they may be mistakenly diagnosed as having iron deficiency anemia. It is estimated that about 200,000 persons in this country carry the trait.

Diagnosis is relatively straightforward in those who have the overt disease, but definitive diagnosis in carriers of the trait is much more difficult and requires relatively sophisticated hematologic tests.

Cooley's Anemia Legislation

The National Cooley's Anemia Control Act passed in 1972 provided for expanded programs of research, diagnosis, prevention and treatment of this disorder. NIAMDD has the primary responsibility for conducting research in Cooley's anemia. However, under the provisions of the National Heart, Blood Vessel, Lung and Blood Act of 1972, a comprehensive national plan for the future research needs in certain blood diseases, including Cooley's anemia, is included in the NHLI's report required under the Act.

Coordination of the Cooley's Anemia Program

The NIH Inter-Institute Coordinating Committee on Cooley's Anemia was formed to assure that the research efforts related to the disease are coordinated into an effective total effort. The Committee's tasks have included identification of high priority research and development areas. Representatives from the various agencies of the Public Health Service involved in implementing the Cooley's Anemia Control Act form the Inter-Agency Coordinating Committee. Activities of these agencies including screening, counseling, education and research are reviewed and coordinated to provide a more fully integrated program. Previous reports have detailed some of the research grants supported by the various awarding units of the NIH and have outlined the research activities of the Molecular Hematology Branch of the NHLI, where the intramural research in Cooley's anemia is performed within the NIH. The present report shows continued progress in the NIH commitment to the support of research in Cooley's anemia. Program coordination has resulted in particularly close cooperation between the two NIH Institutes which have the major responsibility for support of Cooley's anemia research.

Iron-Chelating Agent

Animal trials are now well under way to determine the usefulness of new 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. A wide range of compounds are being evaluated 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 fully evaluated in animals for biological safety and effectiveness.

In a pilot clinical program, ten patients, ages 7-24, are being studied at Rockefeller University, New York, N.Y. for the efficacy of oral 2,3-dihydroxybenzoic acid in aiding removal of excess iron from the body.

Conference on Iron Chelation

A second annual conference of contractors and consultants working on iron chelation was held at NIH in September, 1975, to assess progress and to coordinate their activities. These investigators and experts predict the future development of a safe and effective chelating agent. The results of this conference will be published and the proceedings are expected to be a valuable reference work in this field.

Clinical Testing Using DF

Even though desferrioxamine (DF) is not an ideal drug, it is the only one currently available for use as an iron chelating agent. 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, a less than satisfactory route particularly in small children. In order to evaluate properly this drug, clinical trials are planned by the National Heart and Lung Institute for FY 1976.

Inexpensive Screening Test and Screening Programs

This year the NHLI began funding a pilot research study on screening for thalassemia trait and subsequent counseling for those affected with this condition. The main 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 which is not yet available. The NHLI is now field testing a procedure which might be able to identify both sickle cell anemia and Cooley's anemia carriers, using chromatography techniques.

These research projects are being coordinated with the programs carried on by the Health Services Administration (HSA) of the Public Health Service. The HSA effort and the NIH pilot programs in screening will insure maximum benefit from the knowledge obtained. In addition, the Center for Disease Control (CDC) of the Public Health Service (see below) is active in developing and refining screening techniques for Cooley's anemia. The NIH maintains close contact with the CDC's laboratory program through the mechanism of the Inter-Agency Coordinating Committee.

CDC Report

The Center for Disease Control (CDC) is involved in a number of activities concerned with the laboratory detection of Cooley's anemia including screening techniques and educational programs. The National Laboratory for Hemoglobinopathies organized as part of the Sickle Cell Disease Program of the Department of Health, Education, and Welfare (DHEW) has, since its inception, studied detection of Cooley's anemia as well. Laboratory detection of hemoglobinopathies using the most reliable screening techniques and the development of educational programs in these methods are the focus of the program. Since the first workshop in July, 1972, more than 700 people have been trained in detecting abnormal hemoglobins and thalassemia. Laboratory manuals have also been developed and published. A task force has been formed and has made recommendations to CDC that screening for thalassemia be part of an "Anemia Screening Program".

The Hematology Division of the CDC serves as a collaborating center for Cooley's anemia for the World Health Organization and as the central laboratory for the International Committee for Standardization in Hematology Expert Panel on Abnormal Hemoglobins and Thalassemia. Three international working groups have been organized to develop and/or modify laboratory methods for detecting thalassemia. The World Health Organization has accepted the Panel's recommendation that diagnosis of thalassemia should receive priority as one of four areas of hematology to receive WHO support during the next year.

CDC is thus currently playing an important role in Cooley's anemia--largely one of developing improved methods for the laboratory diagnosis of Cooley's anemia, serving as a national and international reference and teaching laboratory, and as a collaborating center for international laboratory activities in thalassemia.

Intramural Research

Research conducted at the NIH on Cooley's anemia is carried out in the Molecular Hematology Branch of the NHLI. This broad-based program is exclusively involved in the clinical and laboratory study of hereditary anemias, with a primary interest in Cooley's anemia.

The laboratory portion of the Branch has succeeded in synthesizing human hemoglobin in the absence of intact red blood cells. This cell-free experimental system is composed of purified components isolated from human red blood cells. Using this system, it has been determined that the molecular defect in Cooley's anemia is carried by messenger ribonucleic acid (mRNA). Furthermore, the cellular defect of the affected cell can be exactly reproduced using cell-free components from normal cells by the addition of just the isolated mRNA molecule from the diseased cell. This is the first time that the molecular defect of a human genetic disease has been reproduced in a cell-free system.

The laboratory has recently developed an even more powerful cell-free experimental system in which the mRNA itself can be synthesized directly from affected human deoxyribonucleic acid (DNA). This discovery is considered a major advance towards the future understanding and control of Cooley's anemia. Using this system, it should ultimately be possible to discover the exact cause of the defect which results in Cooley's anemia.

In addition to these biochemical studies, the regulation of hemoglobin gene expression in bone marrow cells grown in tissue culture and in somatic cell hybrids is being studied. The mechanism which controls the switching of one hemoglobin gene to another in the intact cell is being investigated in hopes of being able to "switch off" the defective Cooley's anemia gene.

In the clinical program, patients with Cooley's anemia, sickle cell anemia, and other congenital hemolytic anemias are treated and studied. Selected patients with Cooley's anemia receive free medical care as part of a research project at the Clinical Center of the NIH.

Fetal Cells Analyzed For Cooley's Anemia

A recent study indicates that biomedical scientists may be able to use the transabdominal placental aspiration technique, which samples fetal blood cells in utero to analyze the cells for Cooley's anemia and to establish a correct diagnosis of a fetus. Investigators reported only last year that fetal blood could be obtained with this method aided by ultrasonography from women who were pregnant for 18 to 22 weeks.

NIAMDD grantee Yuet Wai Kan at the University of California, San Francisco, and his associates analyzed blood at 20 weeks gestation from a fetus known to be at risk for Cooley's anemia and predicted successfully that the child would be unaffected.

A couple of Sicilian origin whose first child required monthly blood transfusions had requested prenatal diagnosis during a second pregnancy. With a needle, the scientists obtained samples containing fetal red blood cells and performed studies of globin-chain synthesis. Measurements were in the normal range for a gestational age of 20 weeks. Thus, the investigators were able to inform the prospective parents that their fetus was normal or, at worst, a carrier of the thalassemia trait. Subsequent studies on the newborn male infant showed he was not affected with thalassemia.

The study indicates that prenatal diagnosis is rapidly becoming a reality for families at risk for offspring with Cooley's anemia or sickle cell anemia, two of the major inherited blood disorders. The investigators indicate, however, that more experience in fetal blood acquisition and in the establishment of the safety of this procedure is needed.

Education Materials

Nearly one thousand copies of the Proceedings of the Third Conference on Cooley's Anemia, published by the New York Academy of Sciences, were distributed by NIAMDD. The Institute sent copies to each medical school library, medical specialists in the field, and to persons listed by the Cooley's Anemia Foundation as interested in receiving a copy. In addition, literature printed by the Foundation is distributed to the general public by NIAMDD along with the Institute's own Fact Sheet on Cooley's Anemia. A sister Institute at the National Institutes of Health, the National Institute of General Medical Sciences, has available for the general public a pamphlet entitled "What Are the Facts About Genetic Disease?".

Outlook

New programs have been initiated to evaluate known iron chelators and to develop more effective iron chelating agents. Pilot studies in screening and counseling have also begun. In addition, support will continue through extramural research projects and intramural programs conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Heart and Lung Institute. New insights gained from research in Cooley's anemia can yield increased benefits in saving lives of those afflicted and also in providing better understanding of other genetic disorders.

CYSTIC FIBROSIS

The clinical picture of the inherited metabolic disorder, cystic fibrosis, is brighter than it has been in years past, though the exact nature of its basic chemical defect still eludes investigators. Even though strides have been made in alleviating the complications of the disease, more specific and effective methods of its treatment, management, and possibly prevention must still be found.

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 possibly, eventual prevention of this disease.

In addition to investigations carried out at its research laboratories and clinics in Bethesda, Md., 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

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, and Digestive Diseases	$2,525,000	$2,499,000	$2,680,000	$2,892,000	$2,788,000
Health Services Administration: Maternal and Child Health/Bureau of Community Health Services.	1/	1/	1/	1/	
Total	$2,525,000	$2,499,000	$2,680,000	$2,892,000	$2,788,000

1/ Obligations not identifiable.

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 progressive, 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 - the leading cause of death in these patients. The lung changes may also restrict pulmonary blood flow, leading to increased blood pressure in the lung, 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 concerning pulmonary 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 microorganisms, 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.

Pseudomonas Vaccine in Cystic Fibrosis

Infection with the bacterium Pseudomonas aeruginosa is found with disturbing frequency in patients with cystic fibrosis, burns, cancer, and cardiopulmonary diseases. Antibiotic treatment of serious infection is often unsuccessful, and mortality has been reported to be as high as 80 percent when there is pulmonary involvement with this organism.

Active immunization of susceptible patients with Pseudomonas vaccine has been advocated as a possible means of preventing or improving the prognosis. A joint study by the National Institute of Arthritis, Metabolism, and Digestive Diseases, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases evaluated a Pseudomonas vaccine in 34 patients: 22 with acute leukemia, and 12 cystic fibrosis patients.

Of the 34 subjects, 32 had an excellent serum antibody response to immunization with the vaccine. The leukemia patients' responses, however, were generally somewhat weaker and lasted a shorter period of time than those of the CF group. While the vaccine elicited adverse reactions in a majority of patients, the leukemia subjects experienced greater toxicity. The better tolerance of the vaccine by the CF patients may perhaps be due to their long-term antigenic exposure to the organism due to colonization of the airways and sputum. The addition of a corticosteroid (anti-inflammatory agent) to the vaccine mitigated the adverse effects of the treatment.

Despite the excellent serum antibody responses that were measured by the investigators Drs. J.E. Pennington, H.Y. Reynolds, R.E. Wood, R.A. Robinson, and A.S. Levine, vaccination did not result in any significant clinical benefit to those vaccinees with cystic fibrosis. This was not surprising since antibody levels in the serum do not usually correlate well with levels in the respiratory tract tissue where these patients' infections usually begin. In addition, the pockets of resistant colonization and infection so characteristic of long-term respiratory tract disease in cystic fibrosis are less accessible to antibodies circulating primarily in the blood. The

investigators concluded that local respiratory tract immunization rather than systemic may be more useful in CF patients.

The investigators also found that white blood cells appear to be the most important protective factor against Pseudomonas infection. The study suggests, therefore, that optimal treatment may well include white blood cell transfusions and antibiotics intercurrently, with the added protection of Pseudomonas antibody induced in the patient by prior prophylactic vaccination. More extensive clinical trials of this vaccine are warranted to further evaluate this method of treatment.

Pneumatosis Intestinalis in Cystic Fibrosis

In clinical studies by NIAMDD scientists at the Clinical Center in Bethesda, a patient with cystic fibrosis was found to have pneumatosis coli (a condition characterized by thin-walled, gas-containing cysts in the colon) associated with rectal prolapse, an outward protrusion of the rectal mucous membrane. Although there are several factors in CF predisposing to pneumatosis, it has been rarely reported in the literature. The investigators believe this to be the first case of its kind in a cystic fibrosis patient.

Pneumatosis intestinalis is a relatively benign condition characterized by the presence of gaseous cysts in the intestinal wall. It is frequently associated with mechanical intestinal obstruction or with chronic lung disease. Since both of these predisposing conditions are common in cystic fibrosis, it is surprising that pneumatosis intestinalis is not reported more often in patients with this disease.

Investigators Drs. Robert E. Wood, Chester J. Herman, Keith W. Johnson, and Paul di Sant' Agnese found the present case most unusual in that it was preceded by rectal prolapse, an uncommon complication of CF at the patient's age of 18. Rectal prolapse has not been reported previously in association with pneumatosis coli.

In the absence of complications, the condition produces vague symptoms, if any, requires no treatment, and may be diagnosed only incidentally. When complications occur, however, they may include life-threatening conditions like intestinal obstruction, knotting of the bowel, perforation, gas or air in the peritoneal cavity, and hemorrhage.

The full history of pneumatosis intestinalis is not known; spontaneous disappearance of lesions has been reported, as has conversely, the persistence of lesions for many years. Since symptoms are non-specific, the investigators suggest that the diagnosis should be considered in patients with cystic fibrosis, or other chronic lung disease, who have vague abdominal complaints.

Presence of Ciliary Inhibitor in Urine

Grantees of the NIAMDD at the University of Texas Medical Branch at Galveston have isolated a factor from the urine of cystic fibrosis patients that inhibits ciliary action normally seen in such biological systems as oyster gills.

Previous research has identified such a factor in the serum and media of cultured cells derived from CF patients. In those studies, the protein

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responsible for ciliary inhibition was identified as a polypeptide of small molecular weight associated with the antibody immunoglobulin G (IgG) in serum. Speculation that this polypeptide could also be excreted from the urine of cystic fibrosis genotypes led to this investigation by Drs. Barbara H. Bowman and C. McNeely.

Examination of chromatographic patterns of urine from two CF patients and one normal control subject revealed the presence of three-to-four similar proteins, and one electropositive protein fraction in CF urine which was absent in the normal specimen. When this protein fraction was tested on oyster gills, it was found to inhibit ciliary action. Findings such as these could lead ultimately to a simple, more reliable diagnostic test for cystic fibrosis.

Blood Polyamine Alterations in Cystic Fibrosis

Although the basic defect in cystic fibrosis is unknown, there is general agreement that it is due to an inborn error of metabolism transmitted as an autosomal recessive trait. While research efforts have resulted in effective screening tests for detecting carriers of some other genetic disorders, such as Tay-Sachs disease and sickle cell anemia, a reliable method for detecting carriers of the CF trait has eluded investigators.

Now, recent studies by NIAMDD scientists suggest that blood levels of polyamines (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 blood levels of polyamines might serve to detect CF carriers.

To substantiate this theory, Drs. David W. Lundgren and Paul A. di Sant' Agnese of the National Institute of Arthritis, Metabolism, and Digestive Diseases, and Philip M. Farrell of the National Institute of Child Health and Human Development, evaluated polyamine metabolism in cystic fibrosis by measuring the specific blood polyamine, spermine (Spm), and its precursor, spermidine (Spd), in normal control subjects, CF patients, and asymptomatic carriers of the disease. Male subjects in the latter two groups exhibited a consistent and significant decrease in blood spermine resulting in an elevated Spd/Spm ratio when compared to control males. Polyamine levels in female subjects were more difficult to determine due to fluctuations associated with the menstrual cycle, and further work is required to develop comparable Spd/Spm ratios in women.

Interpretation of these ratios suggests that a factor or factors in cystic fibrosis disturbs the steady state of spermine within the circulation. Tissue concentrations of Spd and Spm vary from organ to organ and their synthesis appears to be increased by various hormones, in cells undergoing rapid regeneration, and in neoplastic tumors. To the best of the scientists' knowledge, decreased spermine levels, however, as described in CF patients and carriers, have never been reported previously in human disease states.

The investigators noted that abnormal polyamine levels represent the first chemical demonstration of an alteration in the level of a low molecular weight metabolite in CF carriers. They propose that CF is associated with a definite disturbance in polyamine metabolism, a factor that may be useful in screening populations for carriers of the cystic fibrosis trait.

Enzyme Activity in the Meconium of CF Infants

NIAMDD grantee Dr. Harry Shwachman and associates of the Harvard Medical School have noted numerous abnormalities in the composition of meconium (mucus-like material in the intestine of the full-term fetus) from newborns with cystic fibrosis. The findings could form the basis for a neonatal CF screening test.

Meconium ileus (intestinal obstruction due to plugging of the intestine with thick oatmeal-like material) represents the earliest manifestation of cystic fibrosis. Among the abnormalities found in this type of meconium are an increase in protein, mucoprotein and glycoprotein content; and a decrease in water and total reducing sugars. The investigators noted that these alterations may hold clues to the etiology and early diagnosis of CF.

In studying the action of lysosomal enzymes (tissue-digesting enzymes) and the disaccharidases (enzymes that split the sugar compounds sucrose, lactose, and maltose) found in the meconium of infants, Dr. Shwachman and his associates found a marked increase in enzymatic activity of all disaccharidases studied in infants with CF. Among the lysosomal enzymes, some increased in activity while others decreased. The activity of the enzyme beta-fucosidase in the meconium of CF infants is particularly noteworthy in that by contrast, no activity was observed in the meconium of healthy infants. This pronounced difference in beta-fucosidase activity could be of special value as an alternative test for screening newborns for cystic fibrosis.

Growth Characteristics and Protein Content of Fibroblasts in CF

Previous research involving tissue culture of fibroblasts (connective tissue cells), lymphocytes and other cells has provided key data for elucidating molecular defects in several inborn errors of metabolism. Similar investigations by NIAMDD scientists utilizing cultured cells are now underway in an effort to discover the underlying defect in cystic fibrosis.

In these studies, growth capability and other basic characteristics of the cultured cells are being established. Proliferation rates were determined by three measures of growth: cell number, DNA levels, and total cellular protein. During rapid growth, cell protein production was also assessed by calculation of the protein/DNA ratio.

On the basis of this research, investigators Drs. Philip M. Farrell, J. Charles Pallavicini, and Marta M. Ulane determined that cystic fibrosis fibroblasts are, in fact, capable of normal growth. The fibroblasts showed, however, evidence of metabolic dysfunction and impaired synthesis of collagen, the main supportive protein of connective tissue. The data also indicate that CF cells exhibit a markedly reduced protein/DNA ratio during the most active growth phase of their tissue culture. Since the DNA content of CF fibroblasts was found to be normal, the change in ratio indicates a decreased cell protein level.

The finding of an apparent reduction in protein synthesis during rapid cell division, coupled with the observation that CF fibroblasts fail to induce normal collagen formation, suggests the possibility of a disturbance in the biochemical regulation of protein synthesis in CF cultured cells. Such an aberration could be, potentially, a genetic marker for cystic fibrosis.

NIAID Effort in Research on Cystic Fibrosis

Although the etiology of cystic fibrosis (CF) is still unknown, it is reasonably certain that the disease is not induced by infections or by the immunologic process. However, respiratory infections are important complications of CF and often shorten the lives of cystic fibrosis patients. The National Institute of Allergy and Infectious Diseases contributes a sizable effort to obtaining new knowledge of the organisms and the body's immune defense mechanisms to them.

For example, the staphylococcal bacteria, which are often responsible for respiratory infections during the early stages of cystic fibrosis, are the subject of 12 grants supported by NIAID. The Institute also supports 63 grants, totaling more than $2.6 million, on investigations into the action of drugs that control bacterial infections and in developing and evaluating new antibiotics. In addition, 40 research grants, totaling $1.8 million, support studies of mechanisms by which bacteria develop drug resistance.

Recent studies by Dr. Julian Davies, University of Wisconsin, have led to the characterization of factors involved in resistance to such antibiotics as streptomycin, kanamycin, gentamycin, tobramycin, neomycin, and butyrosin. Through rapid identification of these resistance factors in clinical specimens, a physician should be able to predict which antibiotics will be effective in treating a patient with cystic fibrosis complicated by a bacterial infection. This should, thereby, reduce the risks of trial and error in patient therapy.

Controlling Respiratory Infections

NIAID is actively supporting research on the development of bacterial and viral vaccines. One such vaccine is expected to protect against at least eight different strains of pneumococcal bacteria. Another is being evaluated for protection against the organisms causing atypical, or mycoplasma pneumonia. Several other vaccines are expected to be effective against respiratory viral diseases. These are all in various stages of development and evaluation.

Largely through the efforts of Dr. Robert Chanock's laboratory at NIAID and Dr. Robert Simpson's contract-supported work at Rutgers University, an attenuated vaccine against respiratory syncytial virus (RSV) is now in early clinical trials. RSV is the most serious of all respiratory viral infections in infants and young children, and is a particular problem in hospital nurseries and children's wards where CF patients are most often found.

Many experts recommend routine use of influenza vaccine in CF patients. NIAID has mounted a major effort to improve vaccines now available and a number of different approaches are being tried. These include use of temperature sensitive mutants in live vaccines and recombinant monospecific inactivated preparations.

Vaccines against parainfluenza viruses and adenoviruses are not as far along but are the subject of other studies by NIAID-supported scientists to limit or prevent infections caused by these respiratory disease agents.

In all, NIAID is supporting 39 grants and contracts totaling over $4 million dealing directly with the development of vaccines against acute respiratory diseases.

NIAID is also heavily committed to investigations in other areas that impinge on the control or prevention of respiratory infections. These include studies of such antiviral substances as Amantadine, interferon, and interferon inducers, and of the immune defense mechanisms involved in localizing and resolving infections.

Rather recently, basic studies on viruses have given birth to a new, highly sophisticated technology known as genetic engineering. This technology may some day make it possible for scientists to repair metabolic defects in CF patients through the introduction of new genetic material into afflicted cells and tissues. The NIAID is supporting research on this technology through both its intramural and extramural programs.

In a spin-off of extramural research on asthma, grantees at Children's Hospital Medical Center, Boston, have extended their studies to a consideration of allergies in cystic fibrosis patients. Drs. Harvey Colton and Robert Zeiger have defined the immunologic basis for asthma resulting from occupational exposure to trypsin (enzyme) dust and are now exploring the possibility that pancreatic enzymes used to treat CF patients may actually precipitate allergic reactions in some of these children.

Pseudomonas Research

Intramurally, Dr. Herbert Y. Reynolds and his co-workers in NIAID's Laboratory of Clinical Investigations have collaborated with NIAMDD investigators in evaluating in cystic fibrosis patients a vaccine against the Pseudomonas aeruginosa.

Although injection with this vaccine appreciably increased antibody titers, the clinical course of the disease in the vaccinees was not improved. Therefore, preliminary attempts were made to immunize the mucous membranes of the nose and throat by aerosol spray. The pseudomonas vaccine was evaluated in a small group of cystic fibrosis patients, and, though the daily application of vaccine for a week was well tolerated, no significant increase in antibody titers in parotid fluid or nasal wash was noted.

Results of these studies have not been encouraging, but the scientists emphasize that these trials have been conducted in teen-age or young adult patients, all of whom had advanced CF as well as pre-existing levels of pseudomonas antibodies. The investigators agree that the benefits of vaccination might be better evaluated if young CF patients could be immunized against pseudomonas before they are initially infected with the organisms. Thus, research directed toward early detection of cystic fibrosis in the newborn is of utmost importance.

Three other aspects of pseudomonas infection in cystic fibrosis have been explored by NIAID scientists:

(1) Intensive study of the pseudomonas microorganism itself has been pursued, principally in collaboration with Dr. Charles Zierdt, Department of Clinical Pathology, NIH Clinical Center. The collaborating scientists have found that the peculiar mucoid P. aeruginosa which colonizes the respiratory tracts of cystic fibrosis patients is a single strain. It can be identified by immunological grouping and by the pattern of bacteriophages (viruses) infecting it. Such a finding narrows the spectrum of potentially infecting

pseudomonas organisms and should make specific immunization and antibiotic therapy easier. Moreover, the organism's unique growth requirements in the altered respiratory secretions of cystic fibrosis patients can now be studied directly.

(2) Opsonizing antibodies that prepare pseudomonas organisms for ingestion by scavenger cells called macrophages have been carefully studied. It has been found that the class of serum antibody known as IgG is most effective in enhancing macrophage efficiency. Thus manipulation of lung-secreted IgG might be a way of improving immunity to pseudmonas organisms in cystic fibrosis patients.

(3) In the process of evaluating patients with chronic obstructive lung disease and with persistent pseudomonas in respiratory secretions, NIAID scientists have found a number of young to middle age adults who have sweating abnormalities--a diagnostic clue for cystic fibrosis. Such patients have apparently far-advanced lung disease but are otherwise in good health and have no evidence of pancreatic malfunction. These patients seem to have a limited form of cystic fibrosis involving the lungs and the sweating system, and to be a part of an evergrowing group of adults with degenerative lung disease.

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 may come.

DIABETES

Authorities now estimate that the number of reported diabetic patients is more than four and a quarter million in the United States alone. It is further estimated that another six million Americans are potential diabetics, persons who at present have no symptoms of the disease, but who may develop diabetes sometime during their lives. Because diabetes is not limited to the population of the United States but is found in every geographic and racial group in the world, it is essential, through scientific research, to work towards a cure for diabetes, a better method of therapy, and the means of preventing its 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). Other NIH components, most important among them the National Heart and Lung Institute and the National Eye Institute, also conduct and support research in such long-range complications of the disease as heart attacks, stroke, neurologic defects, peripheral vascular disease, and blindness. Because many Institutes are involved in diabetes-related research, coordination within the NIH is strengthened and augmented by the recently created Diabetes Mellitus Coordinating Committee which includes representation not only from involved Institutes at NIH, but also from all other Federal agencies with diabetes-related activities.

Recent significant research findings revolve around glucagon, the hormone that was isolated from pancreas only 20 years ago. Accumulating evidence continues to incriminate glucagon, not only for mediating "resistance" or antagonism to the glucose-lowering actions of insulin, but also for an important role it may play in regard to complications of diabetes, such as diabetic ketoacidosis. (see below). There have been additional research developments, too, in continuing studies of somatostatin, a hormone first found in the hypothalamic region of the brain, which is capable of suppressing the secretion of many hormones including glucagon.

Diabetes gained heightened national attention in 1974 with passage of the Diabetes Mellitus Research and Education Act, legislation that calls for a broadening of diabetes-related activities, including the preparation of the National Diabetes Plan by the National Commission on Diabetes.

In response to this Congressional mandate, the National Commission on Diabetes recently has completed a plan which provides a blueprint for major initiatives in the effort to find improved ways and means for controlling diabetes mellitus. The Commission's report, entitled "Long-Range Plan to Combat Diabetes," was submitted to the Congress December 10, 1975. The Commission, under the chairmanship of Dr. Oscar Crofford of Vanderbilt University, has provided a plan for marshalling the resources of the medical profession -- research and practicing physicians -- of the involved NIH Institutes, and of representatives of the voluntary health agencies most vitally concerned with diabetes mellitus to attack the problem.

The NIAMDD anticipates playing a major role in this concerted effort to control diabetes, leading in the implementation of the National Diabetes Plan.

Obligations for Programs in Diabetes

	1973	1974	1975	1976 Estimate	1977 Estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, & Digestive Diseases*					
Diabetes Program	$ 8,235,000	$11,132,000	$14,422,000	$14,672,000	$15,905,000
National Eye Institute.....	$ 3,674,000	$ 4,378,000	$ 4,763,000	$ 4,896,000	$ 5,415,000
National Heart and Lung Institute....	$ 3,965,000	$ 3,793,000	$ 5,600,000	$ 7,000,000	$ 6,000,000
Total	$15,874,000	$19,303,000	$24,785,000	$26,568,000	$27,320,000

* Does not include obligations for diabetes-related research projects which are components of the endocrinology, metabolism, nutrition and kidney disease programs of NIAMDD. For example, in FY 1976, this combined item is estimated to represent an additional $11 million.

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 have a strong hereditary component. As a result of the body's inability to metabolize carbohydrates normally (which results from impaired production or activity of the hormone insulin, normally secreted by the beta cells of the pancreas, and from excessive secretion of the insulin antagonist glucagon), 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, carbohydrates, in the form of glucose, accumulate in the blood and, because of their high concentration, overflow into the urine. It appears that as the disease progresses, derangement in the metabolism of fats and proteins also results.

"Juvenile Diabetes" is the severe form of the disease which is generally characterized by onset early in life. This classic type of severe, "brittle" or "unstable" diabetes primarily occurs in children or young adults with a history of diabetes in their families; it is now recognized that it occasionally emerges in adults. If untreated, juvenile diabetes rapidly progresses to a state of grave metabolic imbalance, believed to be caused mainly 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 ketoacids (diabetic ketoacidosis) which may lead to coma and death unless controlled by insulin and other supportive therapy. Patients with juvenile diabetes require lifelong maintenance therapy based on daily insulin injections, which control the more obvious

clinical symptoms and permit 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, leading to the long-term complications of diabetes. These complications involve an abnormality characteristic of diabetes, in the small blood vessels of the body; an accelerated, degenerative process in the large blood vessels akin to atherosclerosis; and a characteristic, irregular degeneration in the nervous system. With the passage of time, these underlying pathologic processes may 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 disorders of the nervous system including impotence.

The majority of patients with diabetes are afflicted with the more common, less severe type termed "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 insulin. Many overweight patients benefit from reducing body weight and all patients must adhere to a proper diet. Some patients with maturity-onset diabetes may, like those with juvenile diabetes, gradually develop serious long-term complications.

Diabetes-Endocrinology Centers

In February 1975 the NIH awarded a $533,293 grant to establish a fifth diabetes-endocrinology center to expand ongoing fundamental and clinical research on this metabolic disorder. Like its four predecessors, the newest center, at Washington University in St. Louis, is supported by the NIAMDD and is under the direction of Dr. William H. Daughaday, principal investigator.

Established where a significant diabetes research program already exists, these centers are designed to foster a collaborative approach to research and to facilitate project coordination among investigators. To accomplish this goal, the grants support scientific and administrative staff, as well as centralized research facilities available to all investigators involved in the programs.

The centers provide a pool of expertise to increase productivity in an active research environment and encourage innovative research ideas from new and veteran scientists. This expansion of research and communication in the field of diabetes will expedite the flow of new scientific findings from the laboratory to the practitioner.

Other diabetes-endocrinology centers, established in 1974, are located at the following institutions: University of Virginia, Charlottesville; Vanderbilt University in Nashville, Tennessee; University of Chicago and the University of Washington in Seattle.

Diabetes Research and Training Centers

The Diabetes Mellitus Research and Education Act provides for the development, or substantial expansion, of centers for research and training in diabetes mellitus and related endocrine and metabolic disorders consistent with applicable recommendations of the National Commission on Diabetes. These centers are to be much more comprehensive than existing research centers, described in the previous section, in that, besides having a strong research component, they will be responsible for training competent professional personnel for research into the disease and for managing patients. These more comprehensive centers will also function to translate advances in the field of diabetes research into improved care for the diabetic.

Such centers are expensive; this was recognized in the authorization for three years funding that was provided in the legislation. Without specific and continuing appropriations for these centers, their establishment and future potential will not be realized. The Commission has recommended funding beginning in FY 77.

The NIAMDD has already begun to implement this section of the Commission's recommendations through the preparation of "regulations" or "guidelines". Once approved, the regulations are to be published in the Federal Register, after which the Institute will prepare and disseminate to the scientific community (contingent upon the availability of adequate funding) an announcement constituting a Request For Applications for the establishment of such centers.

These Diabetes Research and Training Centers, when established, will have a dual mission of contributing to the search for the eventual cure and prevention of diabetes through research, and of contributing to improved care and quality of life for those with diabetes awaiting cure. Once fully established and as an outgrowth of their specific charges, it is expected that these centers will develop plans for community and regional interaction in cooperation with the Public Health Service's Center for Disease Control and other Federal agencies.

Continuing Search for the Cause of Diabetes

The theory that diabetes may be triggered by an infectious process in persons who are genetically predisposed to the disease has gained more and more advocates in recent years. Additional evidence accumulates to substantiate such a theory. For example, in one study, British scientists have reported that eight of ten new cases of juvenile diabetes were preceded by an infection. NIAMDD-supported investigators have found that half the new cases of juvenile diabetes reported in Erie County, New York, during a given period of time had contracted mumps four years earlier. Other Institute-supported scientists have shown that inducing diabetes in mice by encephalomyocarditis (or EMC) virus is influenced by several different genetic factors.

More recently, in January 1976, NIAMDD-supported investigators in Boston and Richmond reported findings suggesting that still another virus, the Coxsackie B_4 virus, could trigger diabetes in genetically susceptible mice. This particular virus, which causes an influenza-like

illness in man, is closely related to the poliomyelitis virus. Drs. Sidney Kibrick of Boston University and Roger Loria of the Medical College of Virginia noted that other mice which lacked the specific inherited factor did not develop diabetes following exposure to Coxsackie B_4 virus. Their findings appear to strengthen the hypothesis that a combination of inheritance and viral infection can initiate diabetes in animals, and possibly in man. Clearly, much more work is needed to determine the true relationship between viral infection and diabetes.

Evolving Role of Glucagon in Diabetes

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 islet alpha cells, stimulates release of glucose from the liver and tends to elevate blood glucose levels. Insulin is secreted by pancreatic islet beta cells.) An excess of glucagon also has been linked to infection, which often results as blood sugar control deteriorates in diabetic patients, and to diabetic ketoacidosis (abnormal accumulation of chemical by-products of metabolism) which requires emergency therapy to prevent severe acidosis and coma.

Administration of the hormone, somatostatin, lowers glucose levels in diabetic subjects by lowering glucagon levels. It has been suggested that somatostatin might prove to be a useful adjunct to insulin, but much more research must be conducted to determine the validity of this suggestion.

More recently, NIAMDD grantees Drs. David M. Kipnis and Marie H. Greider of Washington University, St. Louis, have described a case of diabetes which seems to support the hypothesis that diabetes may be a bihormonal disorder. The patient they described was a 53-year-old woman whose condition changed from mild maturity-onset diabetes to severe, uncontrollable diabetes, not typical of either the classical juvenile or adult forms. High blood levels of glucose and glucagon were found, associated with a glucagon-secreting tumor of the pancreas. Extensive study of the tumor in vivo (and later at autopsy) revealed characteristics consistent with an origin from pancreatic islet cells. An increased concentration of glucagon in the tumor, compared to that of plasma, pointed to the tumor as the source of circulating glucagon. This study is but one of several recent investigations which have linked hypersecretion of glucagon with diabetes (in addition to impaired insulin activity).

Evidence from some animal studies indicates that development of diabetic hyperglycemia (high blood sugar) requires the presence of glucagon as well as a lack of insulin, and that glucagon suppression might help control elevated blood glucose levels (hyperglycemia) in diabetes. Dr. Roger H. Unger of the University of Texas, Dallas, has shown that glucagon suppression by somatostatin either reduces or abolishes hyperglycemia in insulin-deficient dogs. In normal dogs, when secretion of insulin and glucagon was suppressed to unmeasurable levels by somatostatin, hyperglycemia occurred only when glucagon was infused and was reduced when the glucagon infusions were discontinued. In dogs made diabetic by alloxan and then treated with insulin, continuous somatostatin infusion profoundly suppressed plasma glucagon levels and simultaneously abolished hyperglycemia, an effect which persisted even when insulin therapy was discontinued.

When arginine, a potent stimulant of glucagon secretion, was infused into dogs from whom the pancreas had been removed, plasma glucagon more than doubled, indicating the presence of glucagon-secreting cells in tissues other than the pancreas. The source of this extrapancreatic glucagon was traced to the main portion of the stomach (the gastric fundus), where a second type of alpha-like cell was found with secretory granules indistinguishable from pancreatic islet alpha cells.

These findings challenge several long-accepted concepts concerning diabetes. Excess glucagon, as well as mere insulin lack, may be important, if not essential, for development of the full hyperglycemic syndrome; and possibly high levels of glucose (observed in all forms of diabetes) could be secondary to increased amounts of glucagon from pancreatic and/or gastrointestinal alpha-cells. Moreover, insulin suppression of glucagon, rather than direct insulin action upon the liver, could be the mechanism that decreases release of glucose from the liver. Thus, an induced, sustained glucagon blockade might achieve and sustain normal blood glucose levels in diabetics, a goal not always attained by present methods of treatment by insulin injections.

Almost simultaneously, at the University of California, San Francisco, NIAMDD grantee Dr. John E. Gerich obtained evidence indicating that glucagon may be linked to the development of diabetic ketoacidosis, the grave metabolic state of imbalance associated with poor diabetes control. Two years ago an NIAMDD grantee showed that plasma glucagon levels are elevated in human diabetic ketoacidosis and that such levels are correlated with the severity of the ketoacidosis. It has not been known, however, if increased plasma glucagon levels might precede the ketoacidosis or result from it.

Dr. Gerich and associates have shown that plasma glucagon levels rise abruptly in insulin-dependent juvenile diabetics following temporary withdrawal of insulin therapy, and are associated with other chemical changes in the blood which suggest that glucagon is important in the initiation of diabetic ketoacidosis in man. This study indicates that insulin, when present in adequate concentrations, tends to suppress glucagon and its metabolic consequences; deprivation of insulin, on the other hand, appears to result in high levels of glucagon followed by hyperglycemia, followed eventually by ketoacidosis.

Effects of Somatostatin

In a closely related study, Dr. Peter H. Forsham, an Institute grantee at the University of California, San Francisco, has provided further evidence of a role for glucagon in the development of ketoacidosis in juvenile diabetes. Dr. Forsham's group reported that whereas mild ketoacidosis occurs ten hours after insulin withdrawal in such patients, suppression of glucagon secretion by somatostatin prevents development of ketoacidosis after insulin has been withheld.

Thus, while insulin lack per se does not lead to fulminant diabetic ketoacidosis in man, glucagon excess apparently plays an essential part in the development of this condition.

It has been shown that a three-hour infusion of somatostatin in baboons may significantly reduce the number of blood platelets and increase the likelihood of bleeding. In continuing studies, however, Dr. Forsham demonstrated that somatostatin (given cautiously, in much smaller doses) has no effect on either platelet function or the coagulation process in man and that its prolonged administration lacks ostensible toxicity. These results, which are at variance with preliminary studies in baboons, may be attributable to a dose-dependent phenomenon since 5 to 10 times more somatostatin was used in baboons. They may also be due to a species difference. These later findings are supported, furthermore, by the fact that some 200 human subjects have received somatostatin to date without serious toxic effects, including the absence of effects on coagulation and platelet function in more than 70 subjects treated by Dr. Forsham and his associates.

At Tulane University, NIAMDD grantee Dr. Andrew Schally has detected somatostatin in the rat stomach and pancreas in concentrations similar to those in the hypothalamus (a part of the brain where somatostatin secretion was first identified). The hormone has also been found in the small intestines, but in smaller concentrations. It has not been detected in other body organs. These findings indicate that somatostatin may be synthesized in the pancreas and stomach, as well as in the brain, and may be involved in local regulatory mechanisms for pancreatic and gastric secretion as well as in previously demonstrated suppression of secretion of growth hormone in the pituitary gland. Further studies will be needed to confirm this possibility; at the moment, however, the large quantities of somatostatin found in the upper gastrointestinal tract and pancreas rule out the hypothalamus as the sole source of the hormone.

Hyperlipoproteinemia: A New Dietary Approach

Another NIAMDD grantee, at the Joslin Diabetes Foundation in Boston, Dr. John S. Soeldner, has shown that a diet restricted in cholesterol and saturated fat, together with insulin control of blood glucose levels, is more effective than a conventional diabetic diet together with insulin control, in reducing the incidence of hyperlipoproteinemia (high blood levels of fat-protein complexes) in children with juvenile diabetes.

The risk of life-threatening atherosclerosis (a condition in which the lining of blood vessels collects deposits of fatty material) is sufficiently great in diabetic patients that all efforts should be made to reduce any identifiable risk factors. Therefore, the interrelationships between dietary cholesterol content, dietary polyunsaturated/saturated (P/S) fat ratio, and degree of control of blood glucose levels have been studied in 270 juvenile diabetic children enrolled in two summer camps for diabetic boys and girls.

Results indicate that levels of fat in the plasma in juvenile diabetics were elevated upon admission to camp, with 24% demonstrating hyperlipoproteinemia, primarily of type II. Proper control of blood glucose levels, together with a diet restricted in cholesterol and saturated fats, reduced the incidence of hyperlipoproteinemia significantly (to 5%) and more effectively than a conventional diabetic diet with simultaneous insulin control of blood glucose levels. It was concluded that a prudent diet, such as the one employed in Dr. Soeldner's study, should supplement proper insulin control of blood glucose levels.

Thyrotoxicosis and Diabetes

Thyrotoxicosis is a disease condition resulting from overactivity of the thyroid gland. Although an association between glucose intolerance and thyrotoxicosis was first reported over 100 years ago, the importance of this relationship remains unclear. In 1965 NIAMDD-supported scientists at the University of Cincinnati reported hyperglycemia "consistent with diabetes mellitus" in 28 of 51 thyrotoxic patients (57%), and proposed an inherited relationship between diabetes and thyrotoxicosis.

Long-term observations of 22 of these 51 patients by Dr. Harvey Knowles and associates provide further support for this hypothesis, and suggest that initial testing of all thyrotoxic patients for glucose intolerance is advisable. Moreover, all thyrotoxic patients displaying diabetic glucose intolerance after a return to normal thyroid function should be considered to have permanent diabetes until proved otherwise. Seven of the 22 patients (32%) demonstrated glucose intolerance more than 10 years after successful treatment for thyrotoxicosis, and the glucose intolerance appeared to be clinically important in 5 of the 7 patients. In addition, a family history of diabetes, or a history of children with birth weight greater than 4.1 kg (a presumptive sign of diabetes in the mother), or both, was present in 10 of the 22 patients (43%), which is more than double the prevalence for the general population. The investigators advocate testing all thyrotoxic patients for carbohydrate intolerance and closely following those who demonstrate abnormal tolerance.

Devices for Improved Management of Diabetes ("Artificial Pancreas")

Recently, significant advances have been made in the development of artificial devices to control blood glucose levels by automatic delivery of appropriate amounts of insulin. The earliest of such devices utilized electrodes (of the glucose oxidase or fuel cell type) to measure blood glucose, with a transfer of this information through the use of a computer to a pump, which could then inject an appropriate amount of insulin. A large, bedside machine, (about the size of a large television set), developed in Canada and West Germany, is presently being made commercially available in the United States. Clinical studies of patients utilizing this machine will provide invaluable information needed for miniaturization of such devices to an "implantable" size. Several groups of workers in the United States are currently pursuing such development.

There are also other approaches being studied to meet the problem of providing a more physiological supply of insulin (than is possible by the present means of periodic injection) which basically depend on some membranous (semipermeable) sac or tubules containing live, functioning beta-cells able to respond to changes in glucose levels with the production of needed insulin. The insulin then could diffuse out of the membrane and be absorbed into the blood. Other ways to provide release of insulin at the right time in the proper amount may also be possible and should not be overlooked.

Development of such devices is costly, complex, and involves a multidisciplinary approach. Thus, administratively, such efforts can be most effectively undertaken through a research and development contract program and the NIAMDD is now planning to initiate such a program.

Diabetes-Related Research by the National Eye Institute

Because of the serious effects of diabetes on the eye, the National Eye Institute (NEI) places major emphasis on diabetes-related vision research. Investigations supported and conducted by the Institute are aimed at reducing the rate of blindness and visual disability from this disease. The NEI currently allocates 14 percent of its grants and contracts research budget to this effort by fostering laboratory and clinical investigations of diabetes-related eye problems and by supporting the development and evaluation of new treatment procedures.

A major portion of this research is concerned with diabetic retinopathy, the most serious and common visual problem arising from diabetes and one of the leading causes of blindness in the United States. In the more severe, proliferative form of diabetic retinopathy, abnormal blood vessels grow on the retina. As they develop, they may protrude into the clear vitreous fluid in the center of the eye where they may bleed, thereby obscuring vision. The blood may clear after a while, but if it remains long enough scar tissue will form which, as it contracts, can cause permanent detachment of the retina from its normal position.

There are no known means either to prevent diabetic retinopathy or to retard its progression. But two methods of treatment are now used in an attempt to preserve or restore vision lost from this disease.

Photocoagulation, employing intense beams of light, has been used for more than a decade to weld or destroy the abnormal blood vessels to keep them from bleeding. Yet, until recently there had been no large-scale controlled studies to evaluate scientifically the safety and effectiveness of this technique. In 1972, the NEI-supported Diabetic Retinopathy Study (DRS) was begun for the purpose of gaining solid information concerning the value of photocoagulation in preventing severe visual loss from proliferative diabetic retinopathy. Enrollment of over 1,750 patients in this nationwide Study has been completed, and data from the 15 participating clinics are being evaluated frequently.

The second treatment, vitrectomy, is a major new eye operation made possible in the early 1970's by the development of new microsurgical instruments, some of which were supported by the NEI. In vitrectomy, the clouded, blood-filled vitreous fluid is removed and replaced with a clear solution. This procedure is usually reserved for patients who have been blind from severe vitreous hemorrhage for at least a year. But many ophthalmologists now believe that it may be safe and perhaps more effective to perform vitrectomy sooner. Therefore, plans are now being completed for an NEI-supported clinical trial of vitrectomy to determine the optimal time for its use in the course of diabetic retinopathy.

In addition to supporting the development and evaluation of surgical procedures, the NEI funds a wide range of laboratory research aimed at finding other means to prevent or interfere with the development and progression of diabetic retinopathy.

One current investigation involves study of the small blood vessels (capillaries) of the retina. These deliver nutrients and oxygen to retinal nerve cells and carry away metabolic wastes. Abnormalities in the biochemistry and function of capillary cells may contribute to degenerative changes which occur early in the course of diabetic retinopathy.

Recently, NEI scientists were able to isolate cells from the capillaries of laboratory animal retinas and grow them in tissue culture where their biochemistry, growth, and function can be studied. There are two types of cells in the support structure encasing the capillary. In diabetic retinopathy, one of these cell types--called mural cells--degenerates early in the course of the disease. This leaves the capillary with only the second type--called endothelial cells. It is not known whether loss of the mural cells contributes to changes associated with diabetic retinopathy in blood vessels or, conversely, if these changes are a consequence of other factors.

NEI investigators have found that the mural cells, which degenerate in the disease state, actually proliferate in tissue culture. Additional work is needed to determine whether this effect results from influences of the tissue culture medium or from other causes.

The work offers one method for further study of the development and biochemical differences between mural and endothelial cells. This method is considered promising because it provides an opportunity to observe capillary cells in a controlled environment, and it may prove a valuable tool for studying retinal capillary function in health and disease. Information obtained from these studies could lead to a more thorough understanding of the disease process in diabetic retinopathy and perhaps to new means of treating this disorder.

In addition to diabetic retinopathy, other eye complications occur as a result of diabetes, including a form of cataract. Cataracts generally develop more rapidly and at an earlier age in diabetic patients than in other people. In NEI-supported cataract research a few years ago, scientists identified an enzyme (aldose reductase) in the lens which triggers the formation of diabetic or sugar cataract. The investigators subsequently developed and tested in laboratory animals an enzyme inhibitor that delayed sugar cataract formation. The inhibitor, however, was not effective or potent enough for testing in cataract patients. The investigators, now working at the NEI laboratories in Bethesda, Md., are therefore continuing their efforts to develop an improved inhibitor and have recently reported progress toward that goal. They have now demonstrated that flavonoids, substances derived from green leafy vegetables, are more potent and effective in delaying sugar cataract than the compound previously tested. Additional work is continuing and is aimed at perfecting a substance that may be suitable for testing in diabetic patients who have early sugar cataract. The objective is to delay the formation of cataract in such individuals.

In order to understand better the factors that contribute to diabetic retinopathy as it occurs among population groups, the NEI is cooperating with other NIH institutes in a study of diabetes among the Pima Indians. Members of this tribe, who live on the Gila River Reservation in Arizona, have the highest prevalence of diabetes (40 percent) in the world. The NEI study is the first detailed investigation of the earliest detectable stage of retinopathy. The study presents a unique opportunity to gain additional knowledge about the disease which may benefit not only the Pimas but all diabetic retinopathy patients.

Additional studies supported by the NEI at research centers across the country are exploring other aspects of retinal function in health and disease. All have the ultimate goal of improving the early diagnosis and treatment and finding means of prevention for diabetic retinopathy and related diseases.

Diabetes-Related Research by the National Heart and Lung Institute

While the National Heart and Lung Institute (NHLI) does not have a direct programmatic focus on diabetes, it does support investigations which are diabetes-related. The metabolic effects and cardiovascular consequences of diabetes are studied as aspects of NHLI-supported investigations focused on atherosclerosis, hypertension, coronary heart disease, peripheral vessel disease, arrhythmias, heart failure, shock, and thrombosis in man and animals. In addition, epidemiological investigations of coronary heart disease include studies of diabetes as one of the several predisposing risk factors.

NHLI activities related to diabetes may be categorized as follows:

. Scope - Epidemiology and Biostatistics.

Among NHLI-supported activities in this area is the Framingham Heart Disease Epidemiology Study. Initiated in 1949, this study was designed to explore the natural history of coronary heart disease and hypertension as it develops in a general population. The sample: 5209 men and women, aged 30 to 62 years (at entry). In this study, the cohort has been examined with biennial examinations now completed through 18 years of follow-up. Morbidity and mortality from a variety of cardiovascular disorders have been established. Extensive analysis of factors which are related to excessive risk of developing these diseases has been and is being carried out. Among the findings related to diabetes are:

-- Diabetics show an increased morbidity and mortality from all cardiovascular causes. The increase is more pronounced in women than in men. Diabetics have higher blood lipid values, more high blood pressure, more obesity, and manifest coronary heart disease at an accelerated rate as compared to the average. The lower incidence of cardiovascular disease found in normal women prior to menopause compared to the incidence in men of similar age is absent in diabetic women.

-- The incidence of cardiovascular complications was higher in diabetics than in non-diabetics.

-- There was an increased risk of heart failure in diabetic subjects: in men, diabetes imposed twice the risk of congestive heart failure; in diabetic women, the incidence of congestive heart failure was threefold. Data thus suggest diabetes is another discrete cause of congestive heart failure--and that some form of heart muscle disease is associated with diabetes as a result of either small vessel disease or metabolic disorders.

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- Acquisition of Knowledge - Etiology and Pathology.

  Examples of NHLI-supported activities:

  -- NHLI ongoing intramural and extramural research is being carried out on aspects of capillary basement membrane structure in cardiovascular disease--including studies of the membrane ultrastructure, its clinical composition and reactivity. Genetic, metabolic, and immunogenic etiologic factors for diabetic membrane disease are also being explored.

  -- NHLI presently supports research investigations directed toward the development of an animal model of diabetes, either as an inborn trait or experimentally induced. One such effort involves the examination of arterial lipid metabolism in diabetic hamsters and mice (recent findings have demonstrated that increases in hyperlipidemia are a major factor contributing to increased arterial lipid deposition observed in diabetes). Other efforts have revealed, in studies of arterial tissues, numerous abnormalities in diabetic arteries (including presence of increased lipid droplets in endothelial cells). Studies are also ongoing on the influence of diabetes on the cholesterol metabolism of hamsters.

  -- The NHLI supports research on the interrelationships between the metabolic pathways of lipids and carbohydrates and the changes of lipid and carbohydrate biochemistry that occur in diabetes.

- Education and Dissemination of Knowledge.

  The NHLI supports prevention, control, and education activities primarily focused upon cardiovascular disease through its National Research and Demonstration Center (NRDC) Program -- and focused specifically on hypertension within the National High Blood Pressure Education Program. As diabetes is a predisposing risk factor, such efforts are diabetes-related. Examples follow:

  -- NRDC. Secondary and university education efforts involve the development of self-instructional materials on cardiovascular disease, including risk factors and preventative measures for high school students, their parents and for community college students.

  -- NRDC. One component involves the development of a program of continuing education for physicians and other health care practitioners to acquaint them with the latest knowledge and skills regarding the prevention, treatment, and control of cardiovascular disease.

NHLI nutritionists, in collaboration with their counterparts in the U.S. Department of Agriculture, are involved in updating and publishing a new, authoritative nutrient composition source book. This document will provide basic dietary data necessary for research on effects of diet on blood lipids and cardiovascular disease, as well as for research on changes of lipid and carbohydrate chemistry that occur in diabetes.

The NHLI is also exploring how to best use the expertise of behavioral scientists to augment the skills of practicing nutritionists and physicians in efforts to change health-related dietary patterns within the U.S. population to reduce risk from arteriosclerosis and its sequellae.

- Treatment, Management, Services, Delivery of Care.

While the NHLI is not involved in the delivery of health care as such, its clinical trials--such as Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease, (FY 75 support: $12.5 million) the Lipid Research Clinics Coronary Primary Prevention Trial, (FY 75 support: $8.8 million) and the Hypertension Detection and Follow-up Program (FY 75 support: $11.05 million)--include efforts to determine whether reduction of coronary risk factors (e.g. elevated blood lipid levels, elevated blood pressure, and smoking) will prevent or delay coronary artery disease.

Diabetes is an additional independent risk factor for coronary arrtery disease. Since the major risk factors are more than additive--and intensify each other's effects--a smoker with diabetes is much more likely to sustain a heart attack than a non-smoking diabetic. Proof of the efficacy of risk factor modification will be of major importance to the coronary-prone diabetic patient.

OUTLOOK

The comprehensive plan developed by the National Commission on Diabetes represents the first important step in implementing the legislative efforts that resulted in the Diabetes Act of 1974, and the guidance the plan will provide to Federal health agencies should aid greatly in accelerating and coordinating the Federal attack on diabetes.

The past year has been a highly productive one in diabetes research, and the NIAMDD, the NEI, and the NHLI have played vital roles in this progress. Studies conducted in NIH laboratories in Bethesda or supported by the Institutes and carried out at other biomedical research centers have continued to increase in a very meaningful and useful way the body of knowledge concerning this complicated disease. Possibly, in the near future, these new developments will lead to more effective methods of control and management of this disease and, eventually, to the eradication of diabetes as a severe public health problem.

DIGESTIVE DISEASES

The diversity and magnitude of the category of digestive disorders is evident in that it includes diseases of the esophagus, stomach, intestine, colon, liver, gallbladder, and pancreas. Among the well-known disorders in this category are peptic ulcer, hepatitis, cirrhosis of the liver, gallstones, Crohn's disease, and ulcerative colitis. Some of the causes are infections, cancer, alcoholism, genetic defects and reactions to stress.

Even though gastrointestinal tract diseases are among the most common illnesses in the country, many of these ailments are poorly understood. They are second only to diseases of the heart and circulation in the number of physician office visits or house calls they require. Persons of any age may be afflicted with diseases of the stomach and intestines, which most often affect the middle-aged at the peak of their most vigorous and productive periods. The result can be prolonged and expensive hospitalization and outpatient treatment and countless social and emotional problems. For example, ulcerative colitis is of a chronic nature and many patients are afflicted for years. They may have to undergo extensive and repeated treatments, including surgery.

Obligations for Programs in Digestive Diseases

	1973	1974	1975	1976 Estimate	1977 Estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases	$16,240,000	$19,888,000	$24,053,000	$26,176,000	$26,720,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

The economic and social costs of digestive diseases are high. Chronic digestive disease affects at least 18 million Americans and is of enormous economic cost in direct medical expenditures and indirectly in hours lost from work. In a recent year the cost was estimated at $16.5 billion or some $80 for every man, woman, and child. More than 10 percent of the cost of the Nation's 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. Cirrhosis of the liver has become the fifth most common cause of death in men in the United States. Peptic ulcer strikes one of every ten men at some time during their lives.

The National Institute of Arthritis, Metabolism, and Digestive Diseases bears the responsibility for the Government's program of research in digestive diseases. Through numerous grants to scientists at research centers across the country, many ailments of the digestive tract are undergoing investigation. Research progress continued to be achieved through the most intensive and painstaking laboratory experiments and clinical trials this past year.

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, yet gallstone disease ranks fifth among causes of hospitalization. Some 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 Foundation, Rochester, Minnesota, first reported three years ago that long-term oral administration of a primary bile acid, chenodeoxycholic acid, can result in dissolution of long-standing cholesterol gallstones.

One of the causes of gallstone formation is cholesterol oversaturation of the bile in the human body. Cholesterol, a natural component of bile, is kept in solution by two other components of the bile: lecithin and bile acids. When the ratio of cholesterol to lecithin and bile acids is too great, gallstones form. If the concentration of bile acids can be increased, the cholesterol will again become soluble in bile and there will be no reason for cholesterol precipitation and consequent cholesterol stone formation, or, in the case of existing cholesterol stones, there will be a tendency for their dissolution in the bile acid-rich bile fluid.

National Cooperative Gallstone Study

The concept of cholesterol gallstone dissolution by oral administration of chenodeoxycholic acid has gained momentum in clinical research. A national cooperative trial has been funded by NIAMDD which will investigate the safety and efficacy of gallstone prevention/dissolution with chenodeoxycholic acid. The initial testing procedures comprised Phase One. The five-year plan, now entering Phase Two, has been organized with participation of ten gallstone study centers throughout the country with approximately 100 patients to be treated in each center. Dr. Leslie J. Schoenfield, Director of Gastroenterology at the Cedars-Sinai Medical Center in Los Angeles, has been appointed coordinator of this program.

The ten Treatment Centers are: University of California, San Francisco; Yale University Medical School, New Haven, Conn.; University of Minnesota, Minneapolis; Scott & White Memorial Hospital, Temple, Texas; The New York Hospital-Cornell Medical Center, New York; Emory University, Atlanta, Ga.; University of Pennsylvania Medical School, Philadelphia; Mayo Clinic Medical School, Rochester, Minn.; Duke University Medical Center, Durham, North Carolina; and Cedars-Sinai Medical Center, Los Angeles.

Dr. Scott M. Grundy and associates of the University of California, San Diego, have shown that chenodeoxycholic acid acts to reduce the lithogenicity of bile, and dissolves cholesterol gallstones by decreasing the hepatic secretion of cholesterol. It was not previously known if decreased bile lithogenicity results from increased hepatic secretion of bile acids or lecithin, or from decreased secretion of cholesterol.

This finding sheds light on a possible mechanism of action of chenodeoxycholic acid and suggests that relatively low doses might achieve therapeutic effects without significant adverse effects. Such an approach will be considered in Phase Two of the long-term clinical trials of chenodeoxycholic acid therapy. Other investigators (Dr. Leslie Schoenfield, Cedars-Sinai Medical Center and Dr. Irwin Mosbach, Public Health Research Institute) are finding that chenodeoxycholic acid also acts on liver enzymes that control the rate of cholesterol synthesis by the liver and this may be the starting point for altering biliary cholesterol.

Gallstones Dissolved by Combination Treatment

More recent research shows that a combination of phenobarbital and chenodeoxycholic acid may be slightly more effective in dissolving cholesterol gallstones than phenobarbital alone.

Dr. Leslie J. Schoenfield, an NIAMDD grantee, and his colleagues at the Cedars-Sinai Medical Center, Los Angeles, found that chenodeoxycholic acid and phenobarbital, either singly or in combination, significantly decreased biliary cholesterol saturation, but gallstone size decreased significantly only in patients treated with chenodeoxycholic acid alone or combined with phenobarbital. Phenobarbital alone was ineffective in gallstone dissolution.

The investigators found that chenodeoxycholic acid dissolves gallstones by replenishing the bile acid pool and by decreasing hepatic synthesis and secretion of cholesterol. Because phenobarbital has similar actions, they designed a study to compare the relative efficacy and safety of chenodeoxycholic acid and phenobarbital on the dissolution of gallstones. They will continue to compare chenodeoxycholic acid therapy with combination therapy in an effort to investigate further the effect of both treatments on gallstone dissolution.

Obesity and Gallstones

Obese individuals who are subject to gallstones are even more susceptible during a period of active weight reduction and should, therefore, avoid the see-saw of alternately losing and regaining weight, according to studies by NIAMDD scientists at the Institute's Clinical Research Section in Phoenix, Arizona.

It is well-known that the obese tend to have gallstones more frequently than lean persons and that permanent weight reduction and maintenance of normal weight diminishes the risk of developing such accretions. Recent research has linked cholesterol gallstone formation to hepatic secretion of bile supersaturated with cholesterol (lithogenic bile). The specific relationship, however, between obesity and bile lithogenicity had not been fully explored.

Studies of gallbladder bile from the obese now have revealed that bile lithogenicity is consistently increased in the obese state, and increased even further during active weight loss. Once weight is stabilized at a lower level, however, bile is consistently less lithogenic. Thus, the obese person who alternately loses and regains weight and does so frequently and repeatedly throughout life may intensify the risk of developing gallstones.

Gallstone Formation in Monkeys

Dr. O. W. Portman and his associates at the Oregon Regional Primate Research Center, one of seven primate centers supported by NIH, are studying gallstone formation in atherosclerotic squirrel monkeys to understand better the relationship between the two conditions. The squirrel monkey is susceptible to both conditions and is therefore an excellent research model for scientists in gaining insight into the cause and possible connection between these problems in man.

The investigators looked at the therapeutic approaches to the two diseases which sometimes exert different and reverse effects. For example, the use of unsaturated fats and drugs to lower the blood cholesterol level as a protection against atherosclerosis increases the possible risk of gallstone formation. On the other hand certain chemical agents used to prevent gallstone formation, such as chenodeoxycholic acid, theoretically might affect the course of atherosclerosis.

To identify the factors that affect gallstone formation, the scientists varied the type and level of fat, included or removed cholesterol, varied the source of carbohydrate, and added cellulose to the diet. They found that in most cases, those diets that contained cholesterol resulted in the formation of gallstones in monkeys. At this point, however, the investigators are still deliberating over the importance of dietary cholesterol in human gallstone formation.

There are many similarities and differences between cholesterol gallstone disease in humans and squirrel monkeys in such aspects as stone structure, bile composition and physiology, and response to diet. These findings serve to highlight the usefulness of the squirrel monkey as a research model for many diseases that plague man.

Screening for Gallbladder Surgery

Despite its impressive 90 to 95 percent accuracy, the oral cholecystogram (X-ray visualization of the gallbladder) sometimes fails to spot cholecystitis, very small gallstones, and certain neuromuscular disorders of the biliary tract. If patients with recurrent biliary pain and a negative cholecystogram could be managed medically, this would not be such a problem. Medical treatment, however, is generally unsatisfactory in such cases, and even surgery fails to help fully one patient in three.

NIH grantee Dr. Lawrence DenBesten, University of Iowa, Ames, and associates have been using an expanded series of tests: visualization of the biliary tract after injection of the hormone cholecystokinin, a powerful stimulant of gallbaldder contraction, and analysis of bile collected by a special endoscopic technique. Patients whose symptoms recurred after injection with cholecystokinin, or who displayed a greatly reduced contraction, and patients whose bile contained cholesterol crystals or bacteria, or both, were operated upon and were benefited by removal of their gallbladders. This expanded battery of tests has now made it possible to spot the 5 to 10 percent of patients with biliary conditions not detected by oral cholecystogram and to determine who in this group will benefit from surgery.

Cleansing the Gastrointestinal Tract

The standard cleansing procedure in preparing the colon for diagnostic studies includes dietary restriction, purgatives, and cleansing enemas. These are time consuming, often uncomfortable for the patient, and frequently unsuccessful. Castor oil preparations together with enemas have been reported to produce good results in only 32 to 62 percent of cases.

Dr. Arnold G. Levy and associates of the NIAMDD's Digestive Diseases Branch and colleagues at the NIH Clinical Center evaluated the efficacy and patient acceptability of the saline lavage method of cleansing the bowel prior to X-ray examination. They found that saline lavage is rapid, effective, and more comfortable than the standard procedure of castor oil and enemas, and is preferred by most patients.

The researchers randomly assigned 75 patients requiring barium enemas to a control group and an experimental group. Lavage patients ingested four liters of a salt solution. Total preparation required approximately three hours which was 60 percent less than for the control group. The procedure proved to be successful for 85 percent of the patients capable of completing the preparation and was preferred by 76 percent of the patients who had previously experienced a castor oil cleansing preparation.

The two major disadvantages of the lavage method are the inability of some patients to consume an "adequate" volume and the limitation to patients without cardiovascular or sodium balance problems. Lavage patients, however, experienced less overall discomfort, especially in regard to dietary restrictions, loss of sleep, and administration of enemas. Three to one preferred lavage over castor oil.

The investigators' studies suggest that the lavage method may be useful in cleansing the colon of patients with inflammatory bowel disease in whom purgatives are contraindicated. Additional preliminary studies revealed that lavage may also be useful in cleansing the colon for colonoscopy, thereby eliminating two to three days of dietary restrictions.

Crohn's Disease

With additional confirmatory testing, a very valuable diagnostic tool may be finally available with which to evaluate the status and activity of a severe disease of the small intestine, Crohn's disease. This disease, in which the terminal part of the ileum is usually involved and which may lead to intestinal obstruction, fistula formation and growth retardation in the young, is often difficult to distinguish clinically from ulcerative colitis, also an inflammatory disease but of the colon.

Now NIAMDD grantee Dr. Kurt J. Isselbacher of the Massachusetts General Hospital, Boston, and associates have found that a serum enzyme, lysozyme, is increased in Crohn's disease. Moreover, there appears to be relatively good correlation between the level of enzyme and the activity of the disease.

Thus, of the 54 patients with Crohn's disease evaluated, 46 patients with mild to severe disease as assessed by clinical, laboratory, and radiological findings also showed significantly increased serum lysozyme concentration. In the 8 patients in which the disease was inactive, the

serum lysozyme concentration was normal. There were, however, some patients with mild to moderately active disease in which the serum level was normal or only slightly elevated. Thus the test needs further refinement, but it seems to offer promise as a means of monitoring the course and response to to treatment of a disease difficult to assess.

Changes in the Gut

Intravenous feeding as a way of satisfying all the nutrition needs of selected patients has been employed increasingly in hospitals in recent years to feed seriously ill patients, while some patients are even being taught to feed themselves intravenously in their homes. Yet little is known about the effects of the regularly occurring presence (or absence) of food in the gut on normal gastrointestinal structure and function.

NIAMDD grantee Dr. Leonard R. Johnson and associates at the University of Texas, Houston, who have been working with animal models have found that total intravenous feeding is associated with decreases in gastrin levels, in the activity of the enzyme disaccharidase, and in the weights of the oxyntic or acid secreting gland area of the stomach, pancreas, and small intestine. They reported, however, that the changes can be largely prevented if gastrin, the deficient hormone, is supplied externally.

The investigators also compared rats fed orally with rats fed intravenously. They concluded that oral ingestion of food apparently is necessary to maintain the structural integrity of certain tissues of the gastrointestinal tract. They also concluded that the maintenance of normal tissue stores of gastrin must depend on stimuli provided by oral ingestion of food and its presence in the gastrointestinal tract.

Gastrointestinal Hormones

The upsurge of interest in purified hormones which originate in the gastrointestinal tract, both as diagnostic tools and possibly for therapy of selected gastrointestinal disorders (including hormone-producing tumors), has been met initially by the NIAMDD with a contract to obtain limited amounts of the purified hormones for scientists engaged in relevant experimental studies. Further investigation of potentially useful hormones of the gut will be supported as physiologic properties are further identified, purification is accomplished, and potential or promising clinical applications are clarified.

Absorption of Antigens

Exocrine pancreatic secretion, with its complement of enzymes for the digestion of starches, fats, and proteins, may also have an important role in protecting the body from abnormal molecules.

NIAMDD grantee Dr. William A. Walker and associates at Harvard Medical School and Massachusetts General Hospital, Boston, have examined the mechanism by which immunization interferes with the intestinal absorption of potentially harmful macromolecules. Formation of an antigen-antibody complex on the surface of the gut not only seems to prevent binding of additional antigen to gut cells, but it also speeds up the degradation by gut enzymes of the antigen in the complex. These enzymes (proteases) seem to be of pancreatic origin because when the pancreatic fluid is removed from the intestine of immunized rats, the breakdown of antigen is significantly slower than when pancreatic juice is present. This may be an important function of the pancreas--to limit the absorption of ingested antigen and thus prevent the deleterious systemic consequences of antigenic and toxigenic macromolecules.

Simple Treatment for Diarrhea

A simple treatment for the dehydration that accompanies severe diarrhea has proven so successful that it promises to eliminate cholera as a life-threatening condition as well. The importance of the treatment lies in the fact that it enables victims of diarrhea-caused dehydration to overcome that condition simply by drinking a solution of essential salts and sugar. Ordinarily, in cholera, infantile diarrhea, and other such disorders, efforts to restore by mouth the fluids and essential body salts lost by diarrhea and vomiting are unsuccessful. When taken by mouth, the fluids cannot be absorbed through the intestinal walls fast enough to make up for losses that may reduce body weight 10 pounds or more. It was discovered, however, that the presence of glucose sugar in the fluid that is drunk makes for such rapid absorption through the intestinal walls that dehydration can be overcome. The fluids being used in the new treatment contain, in addition to glucose, sodium chloride (table salt), sodium bicarbonate, and potassium chloride. Dr. Norbert Hirschhorn, supported by NIAMDD fundings, has used the mixture to reduce the high mortality from infant diarrhea in a study among Apache Indians on the White River Reservation in Arizona.

Endoscopy in GI Bleeding

Endoscopic examination should be the first method used in the emergency diagnosis of acute upper gastrointestinal bleeding according to a study by Institute-supported grantee Dr. Joseph B. Kirsner of the University of Chicago.

He found that endoscopy provides a more detailed diagnostic picture than do radiographic studies. Endoscopy provided satisfactory information in 109 of 115 patients who underwent emergency examinations for gastrointestinal bleeding. The most common cause of bleeding was hemorrhagic gastritis. In this series, endoscopy was performed with a flexible fiberoptic panendoscope as soon as the patient's condition was stable.

Aid for Bleeding Ulcers

Severe hemorrhage from stress ulcer--a stomach or duodenal ulcer that characteristically develops, and eventually bleeds, under major stress, after extensive surgery or burns, or after use of cortisone-like drugs--can be life-threatening. The hemorrhage is usually massive and available medical treatment has not been regularly effective, surgery often failing to save life. Dr. Sidney J. Wilnawer and associates, NIH grant-supported investigators, Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, report that 75 percent of a small group of patients with active stress ulcers have responded to doses of human growth hormone with control of bleeding and healing. There is some possibility that growth hormone may also be useful for other ulcerative diseases of the gastrointestinal tract.

Gas and Abdominal Pain

"Too much gas" causing abdominal pain and bloating is probably the most common gastrointestinal complaint encountered in medical practice. Lacking adequate objective means of measuring abdominal gas volume, medical science has generally accepted the patient's subjective assessment of his quantity of intestinal gas. Thus, the concept is widespread that excessive gas is a frequent cause of functional abdominal symptoms.

NIAMDD grantee Dr. Michael D. Levitt of the University of Minnesota and associates had previously determined the volume and composition of human intestinal gas by means of an intestinal washout technique. Using this same procedure the investigators now have shown that patients with "too much gas" actually have a normal volume and composition of intestinal gas. Their studies indicate that complaints of bloating, pain, and gas may result from disordered intestinal motility (which interferes with normal passage of gas) in combination with a heightened pain response to gut distention (where gas is trapped locally), rather than from increased volume of gas. The investigators suggest that efforts to reduce the volume of intestinal gas might benefit such patients, even though excessive gas is not their primary problem.

Duodenal Ulcer

Metiamide is a potent inhibitor of gastric acid secretion in duodenal ulcer patients. Use of this new type of antihistamine drug, however, has been associated with a decrease in the normal number of certain white blood cells, or agranulocytosis. Thus, because metiamide contains thiourea, which is known to produce this disorder, agents have been sought which have a similar gastric acid inhibitory action, but which are devoid of this potential toxicity.

NIAMDD grantee Dr. Jon I. Isenberg of the University of California, Los Angeles, and associates have found that cimetidine, a recently synthesized non-thiourea antagonist to gastric acid secretion, is as effective in animal studies as metiamide, and free of significant toxicity. The present studies have shown that cimetidine is markedly more effective than a widely prescribed anticholinergic drug in duodenal ulcer patients, that it does not produce acute side effects, and, thus, it may be of value in the treatment of peptic ulcer. Nevertheless, this possibility must be tested in well-controlled, long-term clinical trials to rule out any possibility of adverse side effects.

Another potent compound to inhibit gastric acid secretion in patients with duodenal ulcers, belonging to the family of prostaglandin compounds, has been examined by NIAMDD grantee Dr. Morton I. Grossman and associates at the Center for Ulcer Research and Education at the University of California in Los Angeles.

When compared with the conventional antisecretory compound, probanthine at its maximally effective dose, the prostaglandin E_2 compound produced a much more profound (essentially complete) suppression of the gastric acid secretion in response to a meal. It was able to exert this effect, when administered orally, for at least two hours and at a dose small enough to prevent changes in pulse or blood pressure. It may act by specifically inhibiting release of gastrin (the hormone which stimulates peptic acid secretion in the stomach). Additional evaluation of prostaglandin E_2 is certainly indicated, as it also may be of therapeutic benefit to duodenal ulcer patients.

Decline in Duodenal Ulcers

For some unexplained reason, doctors are noting a sharp decrease in the number of cases of the most common form of ulcers. NIH grantee Dr. Albert I. Mendeloff of Mt. Sinai Hospital and the Johns Hopkins University School of Medicine, Baltimore, reports that duodenal ulcers, once shown by data from autopsies to affect 1 of every 10 American men by the age of 65, declined from 1960 until the ailment now strikes less than 1 in 20 men.

The duodenum is the first portion of the small intestine, 8 to 12 inches long, located immediately below the stomach. Duodenal ulcers were virtually unknown in Europe prior to 1900. In England there were only 70 known cases during the entire 19th century. But they started increasing around World War I, and by the start of the Second World War they had become an extraordinarily common disease.

Although the mystery remains as to what has caused the decline in duodenal ulcers, the investigator reports that such diseases of the lower digestive tract as irritable colon and inflammatory bowel disease are increasing. Present day conditions or changes in the population at large may not favor the classical pattern of duodenal ulceration, he explains, but rather, perhaps, different forms of malfunction of the gastric acid-peptic enzyme system.

Survey on Research Needs in Digestive Diseases

In preparation for the second national conference on digestive disease held in 1973, the Digestive Disease Program of the National Institute of Arthritis, Metabolism, and Digestive Diseases initiated a program to conduct a long-term survey to identify future needs and opportunities in digestive disease research.

The November 1975 issue of Gastroenterology, the official publication of the American Gastroenterological Association, was entirely devoted to the fruits of that study. NIAMDD also distributed an additional 800 copies of the survey which was based on a series of papers prepared by scientists actively engaged in research in this field.

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 myriad other metabolic functions. Not surprisingly, an organ of such complexity is subject to a great many injuries and diseases.

Bile Acid Test for Liver Disease

NIAMDD grantee Dr. Alan F. Hofmann and associates at the Mayo Clinic, Rochester, Minnesota, have developed an intravenous bile acid tolerance test, which ultimately may prove more accurate in detecting impaired liver function or liver injury than currently used laboratory tests. There were no observable side effects.

The investigators applied this radioimmunoassay test to patients with biopsy-proven liver disease. Results indicate that the intravenous bile acid tolerance test for the detection of liver disease is convenient, safe, simple, and more sensitive than conventionally used tests.

Prototype of an Artificial Liver Assist Device

The prototype of a new kind of "artificial liver" (which can mimic one specific liver function only) has been developed by NIAMDD grantee Dr. Carl F.W. Wolf, New York Hospital-Cornell Medical Center, New York, N.Y., whose device consists of artificial capillaries formed from hollow semipermeable fibers on which rat liver tumor cells are grown. Culture medium circulates within the fibers and nourishes the cells which grow on the outside of the fiber membrane within a hollow plastic container.

By growing rat liver tumor (hepatoma) cells on the fibers, the investigator has developed an artificial liver assist device which is able to metabolize bilirubin, a basic product of the liver. Bilirubin is normally formed from the hemoglobin of worn out red blood cells which is absorbed from the blood by the liver and altered chemically to be excreted in the bile. In the artificial liver assist device, it was shown that bilirubin added to the circulating fluid (which may be replaced by circulating blood) goes through the fiber walls to the growing, captive liver cells, is chemically altered and returned to the fluid.

Similar hollow fiber devices, which resemble a capillary bed of the circulatory system, have been in use for over a decade as artificial kidneys for hemodialysis. Eventually, scientists hope to develop liver assist devices which (though they cannot perform all of the hundreds of chemical actions of a natural liver) could be used as a temporary chemical "crutch" in cases of overwhelming acute liver failure, until the liver recovers again.

New Treatments for Liver Failure

Along similar lines, perfusion of blood through a column of polymer-coated charcoal--a technique developed to remove overdoses of drugs from the blood of suicidal or overdosed addicted patients--has shown some promise in treating acute liver failure.

Dr. Paul D. Berk, Chief of NIAMDD's Section on Diseases of the Liver, helped organize the liver program at an international conference on the use of sorbents in kidney and liver disease held at the Downstate Medical Center, Brooklyn, New York in November 1975. The chemical "blotters," known as sorbents, are substances that extract from blood and bind irreversibly, waste material that can be toxic in liver and kidney failure. Many medical centers throughout the world are using charcoal and similar chemical "blotters" in experiments designed to reduce the frequency of artificial kidney treatments and to develop an effective therapy for chronic liver disease.

Dr. Berk has been studying methods of removing excess bilirubin by hemoperfusion through a column of albumin coupled to agarose (sugar) beads. Too much bilirubin produces jaundice in adults and definitely has been linked to brain damage in infants. His research also has application to disorders of bilirubin metabolism in newborn babies. Dr. Berk's unique liver assist device traps excess bilirubin from blood as it courses through a bed of blood albumin-coated agarose beads. Other scientists, some supported by NIAMDD funds, use columns of polymer-coated, activated charcoal to trap and remove from the circulation other metabolic products which accumulate excessively in blood and tissues during acute liver failure and other intoxications. Dr. Berk's and other scientists' effort may lead to the development of effective detoxifying devices which would help maintain the body's internal chemical balance during temporary metabolic crises, such as acute liver failure, until the natural liver, once recovered, can take over again its essential chemical tasks.

Outlook

This report of research progress in digestive diseases indicates the diversity and productivity of the broad investigations conducted and supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases. The research findings are uncovering promising new scientific leads and approaches for better methods of diagnosis, treatment or prevention for millions of individuals afflicted and disabled with disorders of the digestive tract and its related organs.

KIDNEY AND URINARY TRACT DISEASE AND ARTIFICIAL KIDNEYS

The kidneys play a critical role in the maintenance of body functions. They remove the end products of metabolism (body chemical reactions) from the blood and perform a number of other essential physiologic processes. Uremia results when the kidneys are unable to remove sufficiently the body's metabolic wastes and thus perform their role in maintaining the body's homeostasis. End-stage kidney failure is the common final event of many different kidney and urinary tract diseases. Some 42,000 Americans die each year from irreversible kidney failure although the lives of an additional 10,000 persons are prolonged with treatment through a MEDICARE-funded program of dialysis with artificial kidneys and of kidney transplantation.

The National Institute of Arthritis, Metabolism, and Digestive Diseases is the focal institute at the National Institutes of Health for Kidney research and diseases of the urinary tract. It shares responsibility for certain specialized aspects of kidney research with the National Institute of Allergy and Infectious Diseases.

Obligations for Programs in Kidney and Urinary Tract Disease and Artificial Kidneys

	1973	1974	1975	1976 Estimate	1977 Estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, & Digestive Diseases					
Kidney Disease	$17,726,000	$18,852,000	$21,077,000	$21,410,000	$21,723,000
National Institute of Allergy and Infectious Diseases					
Kidney Disease	1,188,279	1,341,877	1,419,465	1,375,000	1,487,000
Health Resources Administration:					
Regional Medical Programs	2,461,000	5,651,000	5,224,000	---	---
Total	21,375,279	25,844,877	27,720,465	22,785,000	23,210,000

NATIONAL INSITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases
KIDNEY AND URINARY TRACT DISEASE AND ARTIFICIAL KIDNEYS

Research directed against kidney and urinary tract disorders is an important part of the overall program of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). Now in its twelfth year, the Kidney Disease and Urology Program has over 230 active research grants whose awards totaled $14.2 million during fiscal year 1975. More than three-quarters of these grants support basic investigations concerning kidney and urinary tract function and its relation to disease. Both fundamental and clinical studies are being conducted; these are aimed at improving understanding of the kidneys and advancing our ability to prevent, control, arrest or cure the various diseases of the kidney and urinary tract, through research grants and contracts at medical centers, universities, and industrial and development organizations across the nation.

KIDNEY AND URINARY TRACT DISEASE RESEARCH

Approximately one-half of all renal deaths result from three types of kidney and urinary tract disease -- infectious, immunologic, and hypertensive. To achieve a reduction in the number of these deaths, it is essential that researchers find better methods of preventive treatment, earlier diagnosis and more effective therapy through greater understanding of the basic causes and mechanisms of the disorders. The total program of research includes fundamental studies of the kidney and urinary tract, such as: kidney microstructure as related to function, control of sodium excretion, congenital malformation, 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 in other organ systems such as renal osteodystrophy (uremic bone disease) and anemia. While supportive measures for end-stage kidney disease, such as dialysis or transplantation, are life-saving and life-extending, the most desirable objective of kidney disease research is control and prevention.

Experimental Glomerulonephritis

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 salt and mineral 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.

Numerous studies are being conducted to attempt to explain the mechanisms responsible for the reduction of glomerular (sites of blood filtration in the kidney) filtration rate, for proteinuria and for altered control of sodium regulation in glomerular diseases in humans. Recent studies by NIAMDD grantee Dr. Alan Robson at Washington University in St. Louis show that patients with renal disease and proteinuria may have one of three basic types of permeability patterns: (A) a normal pattern, usually seen in patients with mild lesions or in those who have recovered from acute glomerulonephritis; (B) an increase in permeability so that larger molecules of a size normally held back in the blood pass through the glomerulus and are found in the urine. In addition, the clearances of molecules usually present in the urine in only small concentrations, are increased, a pattern frequently seen in patients with severe glomerulonephritis; (C) a decreased clearance of small molecules normally present in urine with a clearance equal to that of inulin (a vegetable starch used in tests to determine kidney function). In certain patients with renal disease, the clearance of these molecules never equals that of inulin; their clearance is sometimes reduced to 50% or less than that of inulin.

Even though abnormalities in glomerular permeability have not been correlated with specific pathologic abnormalities found in renal biopsy, permeability patterns may change spontaneously during the course of the disease process, or as a result of the administration of drugs. Preliminary reports of studies of experimental glomerulonephritis in animals indicate that steroid therapy may correct patterns of glomerular permeability and may improve both renal function and the subjects' chances of survival.

Serum Immunoglobulins in the Nephrotic Syndrome

Although the cause of idiopathic minimal-change nephrotic syndrome of childhood (INS) remains uncertain, it has been suggested from indirect evidence that this syndrome may represent the clinical expression of a primary immunologic abnormality.

Dr. Robson and his associates have compared serum immunoglobulin concentrations in children with INS with those of children with the nephrotic syndrome secondary to chronic glomerulonephritis (CGN). Results indicate that children with INS may indeed have a primary defect in their immune mechanisms, the observed abnormalities being similar to those described in patients with "x-linked immunodeficiency with increased immunoglobulin M (IgM)."

Throughout the period of this study, the nephrotic syndrome persisted in most CGN children, and this condition was often associated with progressive deterioration of renal function. Serum immunoglobulin (IgG and IgA) levels were significantly reduced in nephrotic patients with either INS or CGN. Although these values increased after treatment of INS with prednisone, mean values remained low. On the other hand, serum IgM concentrations in INS averaged more than twice normal before, during and after successful steroid therapy. Patients with CGN did not have equivalent elevations of serum IgM.

The abnormal pattern of serum immunoglobulin concentrations seen in INS patients -- decreased IgG and IgA and increased IgM -- suggests that the primary defect in INS may not be simple leakage of proteins into the urine (because of abnormally increased glomerular permeability) but may be immunologic, and could consist of deficiency in the thymic-cell function that mediates conversion of IgM synthesis to IgG synthesis. Patients with x-linked immunodeficiency and elevated IgM levels have been found to have thymic aplasia and a similar abnormal serum immunoglobulin pattern.

Lithium Effect on the Kidney

It has been established that long-term lithium therapy is associated with the appearance of a defect in urinary concentrating ability. Neither the rapidity of onset of the lithium-induced defect nor its reversibility following the cessation of lithium administration have been well-defined. Studies by Institute grantee Dr. C. Craig Tisher and his associates at Duke University have attempted to evaluate the immediate and short-term effects of lithium on the urinary concentrating mechanism in vivo, to assess the probable site and spontaneous reversibility of any defect that might be observed, and to evaluate the extent to which any adverse effect of lithium might be prevented or minimized by pre-treatment with amiloride (an agent known to inhibit the epithelial effects of lithium in vitro). The results of this research suggest that alterations in the renal concentrating mechanism can occur rapidly following the onset of lithium administration. They also imply that impaired urinary concentration is due, at least in part, to lithium-induced antagonism to the action of vasopressin on the collecting duct.

Chronic Interstitial Nephritis

The frequency with which various potential causes of chronic interstitial nephritis ("pyelonephritis") are operative is not clearly determined. For example, whether or not bacterial infection ever causes renal insufficiency in the adult, in the absence of other primary causes of interstitial nephritis, is widely debated. NIAMDD grantees Dr. Martin Goldberg and Dr. R. Murray of

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the University of Pennsylvania School of Medicine studied 101 patients with interstitial nephritis and have now found that although it is a common form of chronic renal disease, it is rarely caused primarily by infection. Moreover, few patients have "idiopathic" interstitial nephritis, but analgesic abuse (the long-term use of relatively large quantities of acetophenetidin, aspirin, and related drugs) apparently is as common a cause of interstitial nephritis in the United States as it is elsewhere.

The investigators report that interstitial nephritis comprises a significant proportion (33%) of newly diagnosed chronic renal disease, but rarely results primarily from infection. Of interest in connection with the observation that analgesic abuse is not an uncommon cause of interstitial nephritis in the U.S. is that family members other than the patient may also abuse analgesics and suffer from nephropathy. Two of 10 cases in this study had such positive family histories.

Treatment of Renal Stones

In 1973, Institute grantees Dr. Charles Y.C. Pak and Dr. Masahiro Ohata of the University of Texas at Dallas reported that disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP), when added to urine in vitro, inhibits nucleation and crystal growth of brushite, a calcium phosphate salt with a special crystalline configuration which forms the basis for certain renal stones. It had been shown earlier that orally administered EHDP is excreted unaltered in the urine. These findings led to a recent clinical trial of EHDP by the investigators in patients with calcareous renal stones. The researchers have now found that orally administered EHDP inhibits the basic calcium phosphate renal stone formation process without adverse effects and, thus, may have prophylactic value in chronic calcium phosphate stone formers. Except for a transient rise in serum alkaline phosphatase activity and a slight increase in urinary cyclic AMP, no significant side effects were encountered. Intestinal calcium absorption and skeletal bone density did not change significantly. More extensive clinical study and evaluation of its potential toxicity is needed to determine EHDP's ultimate efficacy in the treatment (or prevention of recurrence) of kidney stones.

Urinary Tract Infections

Laboratory and clinical research by Dr. Marvin Forland and associates at the University of Texas at San Antonio has shown the usefulness of the presence of antibody-coated bacteria in the urine as an indicator of the original site of urinary tract infection, often the precurser of kidney disease. These observations have been confirmed independently by others who correlated bacterial antibody-coating with the presence of upper urinary tract infection when using bladder washout techniques.

In further patient studies in Dr. Forland's laboratory, positive bacterial antibody-coating has been found in most patients with chronic pyelonephritis or in patients with acute pyelonephritis, i.e. where there was an active infection in the upper urinary tract, involving one or both kidneys. Twenty-two of their 76 patients who have been followed for up to 27 months to compare their course with the results of sequential examination for bacterial antibody-coating have been found to have persistent infection, relapse or reinfection. These observations showed that there is a persistence of antibody in chronic kidney infection, an absence of antibody in recurrent or persistent cystitis (bladder infection), and the appearance of antibody with invasion of the upper urinary tract (the kidneys).

These investigators have initiated screening studies in a diabetes clinic to investigate the prevalence of urinary tract infection in a diabetic population, to ascertain the incidence of kidney as compared to lower tract (bladder) infection, and to study the relationship of infection to the development of diabetic nephropathy. This patient group will form the core of a long-term study of the applicability of the antibody-coating test in evaluating the efficacy of various therapeutic regimens in urinary tract infections. A collaborative study has been undertaken to evaluate the sequential changes in antibody-coating in women with acute pyelonephritis of pregnancy, who were free of significant bacteriuria on earlier examinations.

Laboratory studies are continuing to define more precisely the correlation of bacterial antibody-coating with urinary levels of specific immunoglobulins, and to ascertain the complement-fixing and opsonic properties of the antibody coating the bacteria.

Diuretics

Furosemide is one of the newer and widely used potent diuretics, whose main action is on the distal convoluted tubule and loop of Henle of the kidney. This drug is usually given to patients with pulmonary edema or edema due to renal failure, and is thought to produce diuresis by inhibiting the action of the sodium-potassium ATPase system. This prevents the reabsorption of sodium in the distal portion of kidney tubules, with a resulting increase in the excretion of sodium and large quantities of water. Recently several reports of transient deafness and one case of permanent deafness have been reported following the use of furosemide. Experimental studies in animals have shown that furosemide produces morphological changes in the stria vascularis of the inner ear.

Grantees of the NIAMDD, Dr. John Najarian and his associates at the University of Minnesota, have reported six cases of permanent deafness encountered in a prospective study of hearing in patients on renal dialysis and transplant patients over a three year period, where in each case, furosemide was being administered at the time of the reported onset of the hearing loss.

In the six cases seen, extensive review of their medical history and drug administration suggested that a period of furosemide administration during impaired or critical renal function was the one factor common to each patient. The onset of deafness was usually insidious and gradually progressive up to six months after the suspected drug administration.

With the experimental evidence that furosemide does induce stria damage and the absence of other recognized causes of deafness in a series of patients, furosemide must be considered the causative agent responsible for the permanent sensorineural hearing loss.

Polycystic Kidney Disease

Polycystic kidney disease (PKD) is an inherited disease whose symptoms are apparent by the fourth decade of life. The disorder progresses relentlessly to chronic renal failure which can be treated only by dialysis or transplantation. Cardiovascular complications, such as hypertension (found in about half of patients with PKD) and stroke, are prominent features of the disorder. It has been estimated that one in 1000 people carry the PKD gene. The last systemic study of this disease was reported in 1957. At the time of these investigations, none of the modern techniques for diagnosis of renal disease, such as excretory urograms with tomography, radioactive isotope scans of the kidney and sophisticated renal function tests, were available.

NIAMDD grantee Dr. Jovan Milutinovic and his associates at the University of Washington are conducting diagnostic tests on patients who may carry the gene for PKD. Since this disease is inherited as an autosomal dominant, 50 percent of the offspring of the affected patients will carry the gene and will ultimately develop the disease. Due to the delayed onset of symptoms of PKD in most patients, the diagnosis is not made until the fourth decade or later. It is anticipated that one or more of the tests in this study will allow earlier detection of PKD carriers. In that case, offspring of affected patients who are not carrying the gene can be relieved of the worry of developing the disease later; on the other hand, those patients who are found to carry the gene can benefit from genetic counselling regarding the advisability of having children as well as from guidance with respect to planning their goals and lifestyles. Early diagnosis will also facilitate better clinical management of the patients, especially with regard to hypertension and kidney infection.

In a pilot study reported by Dr. Milutinovic's group involving twenty offspring of patients with PKD, abnormalities detected by excretory urograms were found to precede more overt evidence of deterioration of kidney function such as decreased urinary concentration capacity, which is probably the first affected kidney function. Renal biopsies in fifteen individuals with negative excretory urograms are being evaluated and correlated.

Evaluation of Research Needs in Nephrology and Urology

Under a contract awarded by NIAMDD, scientists are evaluating the scientific problem areas requiring immediate and long-range future research efforts in the fields of nephrology and urology. These investigators have been engaged to: (1) assess the state of the art in research in these fields; (2) delineate the needs for future basic, clinical, and applied research; (3) evaluate the feasibility of carrying out research in the areas considered significant; (4) consider priorities in approach to the different recommended areas; and (5) produce a detailed working paper resulting from the study, to be distributed to interested scientists and laymen.

ADVANCES IN KIDNEY TRANSPLANTATION

Whereas the NIAMDD has been the principal supporter of research in kidney transplantation, several Institutes of the National Institutes of Health also support research aimed at improving transplantation procedures for various "target" organs. The kidney is the organ most frequently transplanted with tens of thousands of kidney transplantations having been performed throughout the world. Depending on the selection of the donor organ and how close donor and recipient tissue types are matched, between 40 and 80 percent of kidney transplants remain functional after two years. Some recipients who have received a kidney from their identical twin are now in their second decade since receiving a kidney transplant.

Onset of the end-stage syndrome of uremia can be delayed in patients with chronic progressive kidney failure by using special diets. As the condition progresses, however, artificial kidneys become more frequently used and generally enable patients to resume relatively normal lives. Kidney transplantation usually permits the patient to carry on a still more natural life, although he must still receive daily or alternate-day drug treatments to prevent immunologic rejection of the kidney. This chemotherapy must be continued indefinitely in all cases except those involving organ transplants between identical twins. There are frequent complications from continued use of immunosuppressive drugs such as the inability of the body to resist infection in a normal manner.

Research continues to focus on the search for drugs that can suppress the body's immunologic mechanisms, and on improved immunologic matching of donor kidneys with suitable recipients. Transplant rejection is an obstacle to the routine use of kidney transplantation with predictable outcome, and although methods of preserving cadaver kidneys for proper matching with recipients have improved and the problems of preserving kidneys for distant recipients have diminished, improvements are still needed in these areas.

Viral Infection and the Transplant Patient

A large transplantation center operated by Institute grantee Dr. John Najarian and associates at the University of Minnesota screened 132 transplant recipients for viral infections and correlated the clinical course of these patients. One hundred and ten of these patients showed evidence of infection with cytomegalovirus (CMV) uncomplicated by bacterial infections.

The onset of viral infections were almost always accompanied by a significant illness characterized by fever, leukopenia, and renal malfunction. Of 89 patients with cytomegalovirus infections, 83 survived at least three months. Renal biopsies demonstrated typical rejection reactions in all the biopsied patients and renal malfunction usually responded to anti-rejection treatment with corticosteroid or cytotoxic immunosuppressive drugs. Six of the 89 patients with CMV infections died within a month of isolation of the virus.

The investigators found two paradoxical responses to CMV infections in the transplant patients. In the relatively immunocompetent patient, the infection was associated with renal allograft rejection, a prompt antibody response to the virus, and recovery. The severely immunosuppressed patient, on the other hand, cannot make an antibody response and does not exhibit allograft rejection as a cause of renal malfunction. In addition, he may be further immunosuppressed by the viral infection and is susceptible to sequential infections leading to death.

Immunologic Status of Chronic Hemodialysis Patients

The immunologic status of the individual on chronic maintenance hemodialysis is largely unknown. There is a recognized increased incidence of infection in these patients, as well as increased incidence of problems felt to be of infectious etiology. From this information, the question is raised whether, like the patient with renal failure, or the immunosuppressed transplant patient, the patient on hemodialysis is immunologically compromised.

Scientists at the University of Rochester School of Medicine and Dentistry, supported by a contract from the NIAMDD Artificial Kidney Program, recently conducted an evaluation of patients on chronic hemodialysis to assess their immunocompetence. Their findings reveal that the frequency of response of hemodialysis patients to influenza vaccine is identical to that in age-matched normal control subjects and far exceeds the frequency of response of patients with renal failure not on hemodialysis.

The investigators also found that cytomegalovirus (CMV) shedding develops spontaneously in about 15% of older patients on hemodialysis. The antibody development to CMV is no more prominent in this group than in other CMV antibody positive non-shedding individuals. The investigators say their findings indicate that the difference in the way the hemodialysis patient deals

with CMV is not related to the ability to produce antibody, but their findings show that return to hemodialysis and cessation of immunosuppression corrects an immunodeficiency that was present in the transplant recipient, possibly in cell-mediated immunity mechanisms.

The investigators conducted a prospective study of 85 hemodialysis patients which reinforces the evidence that CMV infection has an adverse effect on kidney transplants and may be a major factor in many allograft failures. The investigators found that over half of the hemodialysis patients showed latent CMV infection when tested, but that only 17 percent of the infected patients shed virus while on dialysis and none of them developed clinical illness attributable to viral infection.

Upon transplantation of a kidney from a CMV antibody positive donor to a CMV antibody negative recipient and initiation of immunosuppressive therapy, however, CMV infection was found to be activated, leading to a loss of kidney function, and a significant rise in graft rejections necessitating nephrectomies. The investigators say their study indicates that it is likely the patients acquired the infection at the time of transplantation, perhaps from the donor kidney, and that it is not likely that these infections are disseminated from personnel in the hemodialysis unit or through blood transfusions.

ARTIFICIAL KIDNEY - CHRONIC UREMIA PROGRAM

Advanced kidney failure may be initiated by kidney diseases caused by abnormal immunologic mechanisms, kidney infection, high blood pressure, diabetes, and other systemic diseases, and by congenital abnormalities of the kidney. However it begins, irreversible and potentially fatal kidney failure strikes more than 52,000 patients annually, of which perhaps 10,000 are suitable candidates for maintenance dialysis (or renal transplantation if a matching organ is available).

Patients who do receive dialysis treatment, which continues to be very costly, may experience a number of undesirable complications and must, of course, adjust their lives to the necessity of regular sessions on the kidney machine. Kidney transplantation is a possible alternative, but many patients (especially older ones) cannot withstand major surgery, and even those who do undergo transplantation must be sustained on dialysis until an appropriate donor organ is found. The patient may also need dialysis again if the new kidney is rejected or does not function properly at first. In fact, on the average, approximately one half of transplanted patients return to maintenance dialysis by the end of the third year, post-transplant, because of eventual failure of the grafted organ. Artificial kidneys have other important uses as well: they are used as a means of life-sustaining support in cases of acute kidney failure, and in treatment of moribund patients with accidental or suicidal drug overdosage. In such cases, use of dialysis can be decisive to the outcome.

The Artificial Kidney - Chronic Uremia Program is working to bring about improvements in artificial kidney apparatus and methodologies, to increase their effectiveness, to decrease their initial and operational cost, to improve the rehabilitation of patients treated through dialysis, and to decrease the incidence of long-term clinical complications which may occur in maintenance dialysis. Advancement in all of these areas is still hampered by incomplete knowledge of the basic complexities of the uremic syndrome. Research into the fundamental aspects of the toxic nature of uremia, and basic and clinical

studies into the long-term effects of uremia and chronic intermittent dialysis are critical to the advancement of this important field of investigation and technological development, and are managed and funded by the Institute's Artificial Kidney Program.

At present about 70 research and development projects are supported by contracts with universities, and nonprofit and industrial research laboratories to give a broad approach to these problems of highest priority. The projects are focused on problem areas, including 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 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, and of metabolic wastes and other substances known to accumulate during kidney failure. A large number of research projects are also devoted to the pathophysiology of uremia in an effort to prevent or control complications in patients who have lost their kidney function and are being maintained with the aid of artificial kidneys.

For a decade and a half, dialysis has been used successfully to maintain life in a significant and increasing number of end-stage kidney disease patients (at present -- 22,000). A great deal has been achieved over these years, and clinicians now have an adequate -- though not optimal -- mode of dialysis based on treatment three times each week, each usually lasting six hours. Dialysis therapy, however, is only partially successful in reversing all of the lesions and dysfunctions caused by chronic kidney failure. Patients maintained on dialysis at present exhibit varying degrees of rehabilitation from poor to excellent.

Plans are now under way for the Artificial Kidney - Chronic Uremia Program to conduct a longitudinal nationwide cooperative clinical trial comparing several dialysis therapies on a broader scale and under more controlled conditions than has previously been done. This is necessary because at present there is no reliable, generally accepted body of data to enable physicians to quantify dialysis therapy for particular patients. A primary objective of this study is to develop data which will enable dialysis to be prescribed for the particular circumstances of each patient. In addition, data from the study should permit definition of the lower boundary of dialysis required to maintain patients free of dialysis-induced complications. Another objective is to develop data which will permit definition of the limits within which currently available equipment is capable of shortening dialysis time, thus decreasing the high cost of this treatment, without loss of clinical effectiveness. This new initiative should produce an important body of knowledge upon which the dialysis community of the future can rely, and which would, hopefully, diminish the high cost of maintenance dialysis, for which the Federal Government currently pays out 330 million dollars per year.

Other research and development efforts of the Program are continuing to 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. A high priority for future improvement involves long-term, well-controlled, multiclinic studies to compare the effects of clinical well-being of short-term daily dialysis and long-term periodic dialysis. There is still the need to advance toward a better method of coupling the human circulation to an extracorporeal dialyzing device, as well as to improve the design of the dialyzer itself so as to lower the hours of dialysis from the generally required 18 hours per week to 10 to 12 hours or less.

Scientists in this field must also continue to focus on the prevention of known complications of long-term dialysis, such as bone disease (osteodystrophy), anemia, peripheral nerve damage (neuropathy), and premature cardiovascular death. Particular emphasis is being placed on studies of alterations in patterns of fat and carbonydrate metabolism which occur during the course of long-term dialysis, because these conditions appear to be linked to premature degenerative changes in blood vessels leading to heart disease, the number one cause of death in long-term dialysis, and stroke.

Although morbidity from complications such as osteoporosis, osteomalacia, and hyperparathyroidism have lessened in recent years, many patients maintained with dialysis still 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 of calcium and phosphate from the bone to compensate for low blood calcium levels. Researchers have shown 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. A third factor, related to the uremic patients' inability to utilize vitamin D normally, is discussed below.

Atherosclerosis in Prolonged Maintenance Hemodialysis

The most serious medical problem associated with long-term survival of patients maintained on hemodialysis continues to be the high incidence of atherosclerosis. The evidence today suggests that cardiovascular disease is the leading cause of death among patients undergoing chronic hemodialysis, and is the major factor limiting their survival over the long term.

Dr. Belding H. Scribner and associates at the University of Washington, supported by NIAMDD contract funds, have shown through a retrospective study of 39 patients on prolonged hemodialysis that accelerated atherosclerosis is a major risk. In this study, the incidence of complications such as heart attacks (myocardial infarction), stroke, and refractory congestive heart failure 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 leads to early atherosclerosis and cardiovascular impairment). These patients are exceedingly susceptible to atherosclerosis. The data suggest that the probability of death from such complications increases with time on dialysis, and that dialysis candidates with existing symptomatic cardiovascular disease should receive a kidney transplant if at all possible.

Other studies have also shown that death rates of dialysis patients from coronary heart disease are many times higher than in the general population. Since there is no adequate body of knowledge either to explain or solve this situation, continued investigation of this fundamental medical problem is imperative.

New Wearable Artificial Kidney

Scientists at the University of Utah, supported by a contract from the Artificial Kidney Program, have developed a wearable artificial kidney which may be available for general use within a number of years. The seven-pound device will be a welcome and needed addition to the various types of artificial kidneys currently available. The unit can be produced at a considerably lower cost than conventional dialysis machines, and it promises to make dialysis less expensive and possibly less damaging to the patient's red blood cells. It will also provide the great advantage of freedom of movement to users who presently must spend hours connected to large, stationary machines during conventional dialysis treatment.

According to Dr. Robert Stephen of the home dialysis training center at the University of Utah, where the device was developed, a patient using the portable unit would undergo dialysis every day instead of three times weekly, thereby maintaining a more even chemical balance in his blood and tissues and preventing a buildup of waste products. In its present stage of development, the portable artificial kidney cannot remove urea, a major waste product, from the blood. Therefore, in addition to using his portable unit two hours a day while moving about freely, the patient will spend one hour with the unit attached to a stationary 20-liter tank with dialysate (blood-washing solution) to remove urea.

Treatment of Hypocalcemia

Calcium malabsorption in chronic renal disease has been attributed in part to the affected kidneys' inability to convert the vitamin D_3 metabolite--25-hydroxy vitamin D_3--to its most active form--1,25-dihydroxy vitamin D_3. A number of projects supported by the Artificial Kidney Program has shown that the normal conversion of 25-hydroxy vitamin D_3 to 1,25-dihydroxy vitamin D_3 is impaired or absent in dialysis patients since they lack the natural, normally functioning kidney tissue in which this conversion takes place. Moreover, the administration of small quantities of the latter vitamin D metabolite to such patients can bring about a normal intestinal absorption of calcium from the diet, and tends to counteract the frequently developing secondary hyperparathyroidism. Although administration of 1,25-dihydroxy vitamin D_3 has been found to correct calcium malabsorption, it is still expensive and cumbersome to synthesize, making treatment with it on a large scale unfeasible at present.

Thus, attention has been directed to a recently synthesized analog of vitamin D_3--5,6-trans vitamin D_3. In a recent study, NIAMDD grantees Dr. Hector DeLuca of the University of Wisconsin and Dr. Saulo Klahr of Washington University at St. Louis, and their associates, have shown that short-term administration of 5,6-trans D_3 normalizes intestinal calcium absorption in patients with far-advanced renal disease. The researchers believe it may be useful in the treatment of hypocalcemia in patients with renal failure or on maintenance dialysis.

Research Advances Related to Peritoneal Dialysis

Peritoneal dialysis, a method of abstracting impurities from the blood by 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. New approaches to peritoneal dialysis are currently under study which ultimately may result in smaller and more efficient equipment for this mode of treatment, and in less complicated and costly treatment.

Dr. Christopher R. Blagg and associates at the Northwest Kidney Center in Seattle, Washington, have conducted a comparative study of home peritoneal dialysis with home hemodialysis in comparable patients under the care of a community dialysis program. His experience to date has demonstrated that the cost of treatment with home peritoneal dialysis is essentially similar to that of home hemodialysis with reuse of the dialyzer and is lower than hemodialysis if in the latter method the disposable dialyzer is not reused. The rate of hospital-based, emergency back-up dialysis for patients on home peritoneal dialysis is somewhat higher than the rate for home hemodialysis patients, partly because of technical problems with the new automated peritoneal dialysis equipment, and also because, as a result of patient selection, the peritoneal dialysis patients generally tended to have more medical problems. No new major problems or complications with peritoneal dialysis were noted.

Dr. Willem J. Kolff and associates of the University of Utah School of Medicine have developed a sophisticated new access device to the peritoneal cavity. This experimental device permits a continuous flushing of the peritoneal cavity with dialysate (in contrast to the conventional episodic filling and emptying of the abdominal space with a dialysate solution). Preliminary results have shown that this new approach enhances the clearance of creatinine (one of the uremic waste products which must be removed) via the peritoneal route.

Dr. John F. Maher and associates at the University of Connecticut Health Center, and Dr. Karl D. Nolph and associates of the University of Missouri, have obtained preliminary experimental results that indicate that the clearance of some uremic wastes by way of peritoneal dialysis can be improved significantly by the systemic or intraperitoneal administration of certain vaso-active drugs. These studies are based on the assumption that peritoneal clearance may be increased if the blood capillaries which line the peritoneal cavity can be expanded (or possibly even be made more permeable) with the aid of specific drugs generally known to dilate capillaries or to increase their permeability.

Vitamin B_6 Nutrition in Dialysis Patients

The dietary requirement for vitamin B_6 in maintenance dialysis had not been established heretofore; chronic uremic patients have been reported to be deficient in vitamin B_6. Dr. Joel D. Kopple and associates of the University of California, Los Angeles Schools of Medicine and Public Health, have now demonstrated that a majority of patients on maintenance dialysis who ingest the normal amount of approximately 1 mg. per day of vitamin B_6 in food will be deficient in this vitamin. A daily supplementation of 4 mg. of vitamin B_6 corrects this deficiency.

Trace Element Abnormalities

Dr. Allen C. Alfrey and associates of the University of Colorado School of Medicine, have been studying the composition of tissues of maintenance dialysis patients with respect to the concentrations of trace mineral elements which they contain, and have compared these values with concentrations found in normal subjects. They have found a significantly increased concentration of aluminum in the heart, bone, brain, liver, and skeletal muscle of dialysis patients. The most likely source of the increased body burden of aluminum would appear to be the aluminum-containing phosphate-binding gels routinely administered to dialyzed uremic patients since other environmental sources of aluminum have not been identified. Animal studies are in progress to evaluate better the effect of orally administered aluminum-containing phosphate-binding gels on body aluminum burdens. These studies are of particular interest in connection with the possible causation of a dialysis-associated central

nervous system syndrome which leads to a characteristic speech defect, convulsive seizures, dementia and eventually death. Scientists studying this encephalopathy suspect that it might be caused by an abnormal accumulation of some mineral trace element in the brain and thus far the only consistent and most significant abnormality found in such patients is an increased aluminum content of the brain's gray matter.

Protein Requirements of Patients on Maintenance Dialysis

Dr. Frank A. Gotch and associates of the Franklin Hospital in San Francisco have conducted nitrogen balance studies in maintenance dialysis patients who were given diets containing different levels of protein. They have found that patients maintained on a low protein diet which supplies 0.5 gm. protein per kg. body weight were in negative nitrogen balance; thus this intake is not adequate for chronic dialysis patients despite the fact that this level of protein intake is generally considered adequate for normal nutrition in non-uremic individuals. Patients with intermediate protein intakes (1 gm./Kg.), on the other hand, maintain their nitrogen balance. Based on the day-to-day data obtained in these studies, the dialysis process itself apparently increases protein catabolism on the day of dialysis. The reason(s) for this are obscure at present and warrant further investigation.

Blood Cholesterol Levels in Treatment with Oral Sorbents

Dr. Eli A. Friedman and associates of the Downstate Medical Center in Brooklyn, are studying the use of orally administered oxystarch and activated charcoal in reducing the total body burden of uremic waste products. The principle involved is that these waste products will be selectively absorbed and bound to these sorbents in the intestinal tract (to which they migrate by way of the capillaries lining the gut), and will be carried out through fecal elimination. In continuing experiments they have shown that such a treatment decreases the blood-urea-nitrogen level of chronically uremic patients. There is a simultaneous increase in fecal nitrogen excretion during treatment with oxystarch, but only insignificant further increases in fecal nitrogen excretion were noted during combined treatment with oxystarch and charcoal. An interesting serendipitous finding was noted during these studies; mean serum cholesterol fell in the group from 200 mg% to 166 mg% on the average, and in each patient, during combined therapy with oxystarch and charcoal. It was concluded that, in addition to the previously noted increased nitrogen excretion during oxystarch treatment, the reduction in serum cholesterol observed in this oxystarch-and-charcoal trial may have clinical application in uremic and non-uremic patients in connection with future attempts to diminish blood cholesterol levels to retard atheromatous blood vessel degeneration.

Drug Therapy in Renal Failure

Patients with impaired renal function often require major adjustments in dosage of common therapeutic agents to avoid adverse reactions or further renal damage because of reduced or absent renal excretion of these drugs. An exhaustive literature search by NIAMDD grantee Dr. Cecil J. Coggins of Massachusetts General Hospital, Dr. William M. Bennett of the University of Oregon Medical School, and Dr. Irwin Singer of the University of Pennsylvania School of Medicine has now provided a practical guide to pharmacological management of adult patients in this category, particularly those undergoing regular, periodic dialysis.

The researchers have culled from 472 references in the literature what is known about current therapy with commonly used drugs in the presence of renal failure, and compiled a comprehensive guide that can be used to plan treatment more rationally. Drugs are listed in alphabetical order in five tables, either individually by generic name or under subdivisions based on the major type of pharmacologic action. The tables suggest maintenance dosage intervals for common drugs used in patients with renal insufficiency, and are designed to provide the clinician with rough guidelines on which to base safe and effective therapy, but not as a substitute for clinical judgment. The tables will require constant reappraisal to ensure adequate therapy without toxicity, as well as periodic revision to incorporate information about new drugs and newer data about old drugs.

Conferences, Publications, and Scientific Communication

Critical problems and opportunities in kidney disease research are explored regularly through workshops and symposia organized by NIAMDD or co-sponsored with a particular university research center. In 1975, an Institute-sponsored workshop on benign prostatic hyperplasia, or enlargement of the prostate gland, was held at NIH. This disease affects more than 60 percent of the male population over 60 years of age. Twenty-five papers were presented by scientists from Europe, Canada, and the U.S. to 100 representatives of such scientific disciplines as endocrinology, steroid biochemistry, pathology, and urology. A primary goal of this conference was to stimulate interest in this field among investigators and to encourage scientists in various fields to become interested in urological research.

Also in 1975, the Artificial Kidney Program co-sponsored an international symposium on the use of specific chemical binding agents ("sorbents") in kidney failure and selected cases of acute liver failure. The major thrust of this conference which brought together about 150 scientists from the United States and abroad at the Downstate Medical Center, was the use of such sorbents in the direct purification of blood of uremic patients in a process -- hemoperfusion -- in which blood passes directly through a mixture of sorbents which trap and select out of the blood undesirable, toxic waste products. Another major and novel use of sorbents is in dialysis where they are used to regenerate the blood purification solution (dialysate) in artificial kidneys. The proceedings of this conference will be published in the journal KIDNEY INTERNATIONAL to effect a broad dissemination of the latest research findings in this area which is strongly supported by the Institute.

Each year 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 a quarterly 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 popular publication is now being enlarged into a new, comprehensive publication, Kidney Disease and Nephrology Bibliography, a bimonthly which will cover the field of kidney disease and research related to the kidney and urinary tract.

The Institute also distributes pamphlets about kidney disease, dialysis, and kidney transplantation.

Transfer of Data from the National Dialysis Registry

Data gathered by the National Dialysis Registry, organized and maintained by the Institute's Artificial Kidney Program, now covers about 80 percent of the individuals receiving dialysis treatment in the United States. Since its implementation in mid-1969, the Registry has accumulated data on patients treated in approximately 500 dialysis programs throughout the country.

Beginning in April 1976, the collection of the various kinds of data on dialysis patients as well as on patients receiving and donating transplant organs will be assumed by the Medical Information System for End-stage Renal Disease Patients of the Health Services Administration's Bureau of Quality Assurance. The National Dialysis Registry, now being phased out, will transfer its data to that Bureau, as will the NIH-American College of Surgeons Organ Transplant Registry, which previously collected data on organ transplantation under support from a consortium of NIH Institutes.

The National Institute of Allergy and Infectious Diseases Research Effort in Kidney Disease

The National Institute of Allergy and Infectious Diseases (NIAID) focuses research attention on the causes, prevention, and treatment of kidney diseases. The Institute is the focal point for research on the development of ways to minimize rejection of transplanted kidneys. The hope of the future for kidney disease studies lies in a better understanding of allergic, immunologic, and infectious processes. Accordingly, this first report on NIAID's involvement in programs concerned with kidney disease research includes a description of some past discoveries on which current investigations are based.

Glomerulonephritis

A number of studies have increasingly demonstrated the role of the immune system in the disease process leading to glomerulonephritis. Until recently, the cause of this kidney disorder was unknown and only clinical observations suggested an association with preceding infection. We now know that glomerulonephritis is not an infection of the kidney per se but rather results from an untoward side effect of the body's defense mechanism.

In response to the entree of a foreign material (antigen), a highly specific protective substance, antibody, is generated by lymphocytes and plasma cells. As a result of interaction of antigen with specific antibody, aggregates of molecules (complexes) are formed and circulate. Some of these complexes lodge in the kidney's filtering bed (the glomerulus) and incite inflammation within kidney tissue.

Much of this knowledge has come from research carried out by Dr. Frank J. Dixon and his associates at Scripps Clinic and Research Foundation, La Jolla, California, who are supported by a NIAID program project grant. Two major mechanisms responsible for the development of glomerulonephritis have been found: (1) in some cases, antigens from outside the body, such as bacteria and viruses, initiate the process leading to deposition of complexes, and (2) in others, membrane tissue of the kidney becomes altered by disease and actually serves as the inciting antigen.

In the development of an animal model (the rabbit) for the first mechanism, Dr. Dixon has shown that chronic viral infections are important not only for their infectivity per se but also because of the manner in which they participate in the formation of large circulating complexes that deposit in the kidney. When these viral complexes occur during pregnancy, they can in some cases be transmitted to the fetus and deposited in the kidneys.

In the case of the second type, i.e., autoimmune nephritis, the chemical nature of the affected kidney membrane has been described by the Scripps group, thus allowing for appropriate diagnostic procedures.

Since almost 60% of kidney transplants are carried out in glomerulonephritis patients, there has been some concern that failure of the transplanted kidney might be due, not to the immunologic mechanisms of graft rejection but to damage to the kidney by the immunologic mechanisms which led, initially, to glomerulonephritis. To help resolve this question, NIAID has been supporting under contract, the examination by Dr. Dixon and his associates of renal biopsy and/or serum specimens submitted by kidney transplanters.

Since the inception of this contract in 1969, specimens have been submitted for study by 121 institutions on over 4,000 nephritis or transplanted patients. During the past contract year, 524 renal specimens (149 from transplanted kidneys) and 2,075 serum samples from 955 patients were submitted for immunopathologic analysis.

Using immunofluorescent, radioimmune, and antigen or antibody elution and binding techniques, the contractors have been able to screen these specimens and classify many different kidney conditions according to the patterns and types of antibody and immune complexes deposited on the renal tubules and glomeruli. This diagnostic classification has greatly aided attending physicians in making decisions regarding the timing and type of therapy most suitable for an individual patient.

Dr. Dixon's techniques are now being applied in collaborative studies at a number of transplant centers to see whether these immunopathological tests, in the hands of other investigators, can predict end-stage renal disease and graft rejection.

Another advance in understanding glomerulonephritis and other kidney disease has been the demonstration of inflammatory-inducing factors derived from: (1) complement, a normal component of blood, and (2) enzymes contained in normal white blood cells (leukocytes). When the foreign antigen combines with antibody, a cascade of blood components known as the complement system is set into action. Some products of the complement reaction and some derived from breakdown products of leukocytes generate further inflammation and injury within the kidney. At Scripps, Drs. Hans J. Mueller-Eberhardt and Charles G. Cochrane have provided important leads for the development of methods capable of diagnosing and counteracting the injurious effects of complement. For example, an understanding of the mechanism of complex deposition in the kidney filtering membranes has already led Dr. Curtis B. Wilson of Scripps to develop experimental methods, whereby harmful products may be removed by reversing the mechanism of their formation.

At the University of Minnesota, genetic studies have demonstrated that specific hereditary deficiencies of complement components may predispose an individual to the development of glomerulonephritis. Dr. Alfred F. Michael's

laboratory techniques have identified specific components of kidney tissue which, when under the influence of infectious agents or disease processes, can, in turn, result in nephritis. Additionally, studies on long-term circulation of immune complexes have demonstrated that variations in the type of nephritis may be determined by a corresponding variability in the immune response of the individual.

One of the earliest clinical observations of glomerulonephritis was its appearance in association with and/or following streptococcal infections. For this reason, streptococcal products were at first thought to have some special toxic affinity for localization and injury to kidney tissue. Studies of animal models, however, as well as clinical findings, have implicated an immunologic-hypersensitivity mechanism. Evidence now points to the streptococcal product acting as antigen, generating circulating antibody, and resulting in an interaction capable of deposition and injury to the kidney. This has been especially prevalent following streptococcal throat and skin infections, and scarlet fever.

Recent work at the University of Minnesota by Dr. Louis W. Wannemaker has identified the presence of streptococcal antigens and their derivative immune complexes in urine, blood, and kidneys of patients with post-streptococcal glomerulonephritis. Using immunologic techniques, scientists have shown that the tissue proteins excreted by damaged kidney cross-react with streptococcal products. The ability to identify streptococcal products and fractions and the immune response to them is helping to explain the type of bacterial infections requiring control in the prevention of acute glomerulonephritis.

Pyelonephritis

Pyelonephritis, usually caused by bacterial infection of the pelvis of the kidney, has long been of interest to the NIAID. Bacteria in the urine is being investigated by a number of NIAID-supported researchers who are examining the problem of infection caused by a wide array of bacterial agents.

At Stanford University, Dr. Kenneth Vosti has been studying women with urinary tract infections. He has characterized antibodies to urinary pathogens as well as the antigenic makeup of the infecting microorganisms, particularly E. coli strains. A significant rise in certain serum antibodies specific to the infecting organisms was found in acute pyelonephritis, but to a much lesser extent in cystitis. The patterns of the natural history of these infections are beginning to emerge more clearly and could explain why cystitis becomes a chronic problem.

Dr. Lucien Guze at the University of California, Los Angeles, has found evidence that enterococcal pyelonephritis, in a rat model system, may be mediated by an immunologic mechanism. It was also observed that the development of ascending pyelonephritis could be correlated with virulence of the infecting organism. The cell-mediated immune response to the infection is under careful and continuing scrutiny to shed light on mechanisms involved.

Studies on means of preventing pyelonephritis are being conducted at Tulane University by Dr. Gerald Domingue. This investigator is developing a potential candidate vaccine using the common antigen (CA) isolated from certain intestinal bacteria (enterobacteria). He has demonstrated that, in a rabbit model, immunization with specific fractions of the CA from strains of the bacteria created a measurable protective effect against kidney infections following intravenous challenge. Bacteremia in infected animals was also cleared more rapidly in those with increased levels of antibody against the CA antigen.

The evidence thus far that antibodies against the CA of enterobacteria elicit protective activity in experimental pyelonephritis has far-reaching implications. Indeed, isolated and purified CA material may eventually serve as a useful immunizing agent for conferring immunity against pyelonephritis infections.

An intensive study on experimental pyelonephritis by Dr. Abraham Braude is underway at the University of California, San Diego. The ultimate objectives of the study are to prevent kidney damage in pyelonephritis by improving the immune response. Dr. Braude's experimental pyelonephritis model in the rat suggests that the unique characteristics of the interior of the kidney, with its high concentration of sodium, urea and hydrogen ion, result in a condition that can inactivate certain aspects of the immune response to the detriment of the individual.

Urinary Tract Infections

An intense investigation of a substance found in prostatic secretions of normal men may produce results directly applicable to the control of urinary tract infections. Dr. William Fair at Stanford University has identified an antibacterial substance in prostatic secretions of men and in washings obtained from the normal external vagina. This material -- PAF -- has been partially characterized as a low molecular weight protein with a high zinc content. PAF has a pronounced antibacterial effect and it has been found that patients with prostatitis have significantly lower concentrations of zinc in their prostatic secretions. The work done by this investigator and his group is innovative and will undoubtedly lead to a better understanding of the development of urinary tract infections and their relation to bacterial colonization of the genital tract.

The problem of recurrent urinary tract infections in women is the research interest of Dr. Thomas Stamey, also of Stanford University. This urologist has centered his investigation on the problem of bacterial colonization of the vaginal vestibule. He has shown that colonization of the vestibule by intestinal bacteria generally precedes the onset of urinary tract infections. Furthermore, the organisms colonizing the perineal area are frequently identical to those responsible for the subsequent urinary tract infection. In an animal model system, Dr. Stamey has also shown that hysterectomy is associated with a significantly high rate of vaginal colonization. The adherence of the bacteria to cells of the vaginal mucosa may be the key determinant in this type of urinary tract infection.

Wegener's Granulomatosis

For a number of years Drs. Sheldon M. Wolff and Anthony Fauci of NIAID's Laboratory of Clinical Investigations have been studying the largest group of Wegener's granulomatosis patients in the world. The cause of this disease is unknown but it usually involves the kidneys and, untreated, is rapidly fatal.

Over the past several years, the LCI investigators have firmly established a form of drug treatment which produces long-term remissions in Wegener's granulomatosis which can now be considered cures. The drug, cyclophosphamide, is also used to treat malignancies and to prevent rejections of kidney transplants.

Studies by Drs. Fauci, Wolff, and others on the immune response of Wegener's granulomatosis patients and on the effects of immunosuppressive therapy have relevance for the mechanisms of a wide variety of kidney conditions and to the whole question of immunosuppression in man.

In addition, Dr. Fauci, Dr. Wolff and Dr. James E. Balow have successfully demonstrated the feasibility of renal transplantation for Wegener's granulomatosis patients who are in clearcut remission from disease but whose kidney damage before treatment made long-term hemodialysis a necessity.

Other Kidney-related Research

One of the most exciting research findings of the past year was identification by a team of NIAID scientists of a receptor for complement on the glomeruli -- the kidney's filtering bed of blood vessels.

This receptor for complement has been observed in all apparently normal kidney tissue examined. The investigators have not been able to find the specific receptors in patience with immunologic renal disease, indicating that the receptors in these patients have been covered up by immune complexes. In contrast, there was no loss of receptors in patients with nonimmunologic renal disease. This suggests that the receptors for C3b may play an important role in the localization of complexes of antigen-antibody and complement with the attendant inflammation which leads to the renal lesion.

The initial finding of the C3b receptor in the human kidney glomeruli has now been confirmed by 8 other laboratories. The NIAID work was carried out by Dr. Michael Gelfand of Georgetown University Medical Center, a guest worker in NIAID's Laboratory of Immunology; by Dr. Ira Green of the Laboratory of Immunology; and by Dr. Michael M. Frank of NIAID's Laboratory of Clinical Investigations.

At Johns Hopkins University, Dr. William D. Hillis has been concerned with recognition of viral hazards threatening patients with known renal disease. Using immunologic techniques, Dr. Hillis has identified herpes, hepatitis, and cytomegalovirus in end-stage renal disease and found some evidence that these agents -- though not causing kidney disease -- are related to the altered immune state seen in some patients on hemodialysis.

Type B viral hepatitis in hemodialysis centers is a major medical and public health problem. Recent epidemiologic studies indicate that the annual incidence rate of infection is close to 50% in patients and 20% in staff. Family contacts of patients are at increased risk of contracting viral hepatitis. Although available evidence suggests that hyperimmune globulin may be effective in reducing the incidence of infection in patients and staff, repeated inoculations of globulin at 3-4 month intervals may not be desirable.

The NIAID has been actively engaged in developing a hepatitis B vaccine which has been shown to be safe and effective in tests in subhuman primates. Following further testing, the preparation may be made available for clinical trials in the hope that it will eliminate type B hepatitis as a problem in hemodialysis centers.

Other viral infections which are particularly serious in immunosuppressed kidney transplant patients are herpes simplex, varicella zoster, and cytomegalovirus. NIAID is currently supporting collaborative studies of the efficacy of antiviral substances such as interferon and ara-A in the treatment of these infections and results to date are encouraging.

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Studies by Dr. Giuseppe A. Andres -- a NIAID grantee -- at SUNY, Buffalo have shown that a type of kidney injury, heretofore thought to be characteristic of organ transplantation, can also occur in patients with kidney diseases. This injury to kidney tubular cells is the result of the development of self-produced antibodies to normal tissue. Furthermore, it has been found that glomerulo-nephritis due to immune complex deposition can change into an autoimmune process directed against kidney membrane. Dr. Andres' work emphasizes the importance and need to develop effective preventive and treatment measures for adverse immune reactions following infection and serum sickness.

Kidney damage is occasionally seen as an untoward side effect of some medications. In the case of penicillin, Dr. Curtis Wilson of Scripps has shown how the derivative agent, by inducing allergic mechanisms, can result in specific type damage to the kidney interstitial tissue. Direct application of these data to antibiotic treatment of infections can be useful in medical practice.

Interstitial nephritis is recognized as an important clinical entity. Scientists in NIAID's Laboratory of Clinical Investigations are developing a model of this disease in the guinea pig for two specific purposes: 1) to clarify the mechanisms of interstitial nephritis with respect to the body's two immune processes; and 2) to evaluate the efficacy of various immuno-suppressive regimens on the disease process.

Studies on the association of nephritis with immunologic consequences of bacterial and viral infections have been extended to parasitic infections. Dr. Robert M. Lewert and colleagues at the University of Chicago, in studying hyper-sensitivity and resistance in schistosomiasis (a parasitic blood fluke disease), have reported finding antibody-type globulins and complement deposition in kidneys. This finding favors the concept that renal damage in schistosomiasis may be due not to the infecting organism itself but rather to immunologic reactivity, thus offering leads for the development of effective control and treatment measures.

OUTLOOK

Research and development supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Allergy and Infectious Diseases continue to be major contributors to the growing knowledge and technology imperative to combating kidney disease. These programs can be expected to advance understanding and initiatives in this field even more decisively following current evaluation of research needs in nephrology and urology. Every effort is being made to insure that the impetus of this vital work in research, prevention, treatment and education is directed and carried through to meet effectively the dire challenges still confronting us. The total program to reduce kidney disease, combined with the highest priority research, should yield maximal benefits in prevention and in lives saved.

HEALTH RESOURCES ADMINISTRATION

Bureau of Health Planning and Resources Development
Kidney Disease and Artificial Kidneys

The development of methods of care delivery to end-stage kidney disease patients has been included in the projects supported by regional medical program grants that were made by Division of Regional Medical Programs (DRMP). These grants are in their final year of support in FY 1976 and are now administered by the Bureau of Health Planning and Resources Development (BHPRD) as a result of the passage of The National Health Planning and Resources Development Act of 1974 (P.L. 93-641). These activities were authorized under the 1970 Amendments to Title IX of the Public Health Service Act which encourages regional cooperative arrangements among health and medical institutions to make available to patients the latest advances in the prevention, diagnosis, treatment and rehabilitation of persons suffering heart disease, cancer, stroke, and kidney disease. By these means, and the promotion of regional linkages to improve care, DRMP has attempted to improve the quality and enhance the capacity of the health care system to provide patient care services.

The development of hemodialysis and transplantation over the past decade as complementary methods of end-stage kidney disease patient care has presented a striking opportunity to organize highly integrated systems of care delivery. The characteristics of finite patient population in end-stage kidney disease, and finite therapies represented by dialysis and transplantation, have given care providers a closed system through which to observe the effects of service patterns altered from traditional health care delivery practices. The objective sought is delivery of high quality care to patients whose illness requires complex and high cost treatment, and for which there has been neither funding nor treatment facilities readily available. The responses to these constraints have indicated increasingly practical methods to deliver lifesaving end-stage kidney disease therapy, and promise to offer useful alternatives in the delivery of other high cost radical medical treatment.

Through developmental and demonstration projects, the performance of hemodialysis in the hospital environment, in low overhead facilities outside the hospital structure, and in the patient's home has proved medically effective.

Collateral developments in techniques of organ harvesting, preservation, and transplantation have made renal homotransplantation a practical method of end-stage kidney therapy. Kidney transplantation is increasingly accepted as preferred therapy for end-stage kidney disease because of its potential for full patient rehabilitation and the opportunity for patient egress from rigorous chronic dialysis treatment.

Experience in the development of these therapies has demonstrated that efficient delivery of dialysis therapy requires concentration of the expensive dialyzers and dialysate delivery systems at central points where medical and allied health personnel can be optimally employed in treating large numbers of patients. Similar centralization of kidney transplantation services is indicated to effectively utilize surgical facilities and the specialized services required to back up radical surgery. Thus, the most effective delivery system of end-stage kidney treatment requires aggregates of hospitals and other health facilities interrelated in an organized manner which assures patient access to high quality care through interdigitation of patient referral, patient registry, alternatives of dialysis and transplantation, organ procurement, laboratory services, specialized health and social services, and continued patient follow-up.

Such a system lends itself to coordinated dialysis-transplantation networks which capitalize on existing facilities, the capabilities of nonphysician personnel, and self-care by the patient. A high proportion of patients accepted into dialysis therapy can be trained to perform this treatment in their homes with the assistance of a family member. Such patients can be treated at a fraction of the cost in chronic in-center dialysis. For instance, a 3-bed dialysis facility which might be dedicated to treatment of six patients a year on a chronic in-center basis can potentially extend treatment to up to 36 patients a year, under present practices, by training the patients to perform self-dialysis in their homes, and can also expand the geographic area which the unit can serve. Limited care dailysis, most appropriately established in dense population areas, permits the extension of dialysis care to patients away from high overhead hospital facilities. Limited care dialysis is particularly appropriate to patients whose socioeconomic status prohibits their treatment in a home environment. In the delivery of transplantation services, economics of numbers can be achieved through centralization which realistically permits populations of 2-4 millions to be effectively served by a central complex of services offered through one or more hospitals.

While selective units perform considerably above the average, nationally, patient mortality averages about 10% per year on dialysis. Average mortality rates after transplantation are higher but the normal life that a successful transplant can provide frequently outweighs the increased mortality risks. In most cases, a patient whose transplant is a failure can be returned to dialysis and be transplanted again at a future time. The two year graft function rate for transplant varies between 45 and 85%, depending on the selection of the donor organ. Evidence suggests that rejections then occur at a rate less than 5% per year. There is considerable regional variation in success rates throughout the country. Implementation of well-developed renal plans, as previously described, shows promise of improving the quality of care being provided in many areas.

The realization of these potentials in the provision of end-stage kidney disease care capability has been the focus of the DRMP kidney disease control activity, and has provided the foundation on which the coverage of end-stage kidney disease treatment has been developed under Title II of the Social Security Act.

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

	1973	1974	1975	1976	1977 Estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, & Digestive Diseases	$7,896,000	$8,616,000	$9,632,000	$9,645,000	$9,295,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

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 this field is now viewed with an unprecedented sense of urgency. Health problems such as scurvy, pellagra, beriberi and rickets which no longer menace American people still plague many foreign populations.

The United States, however, is not exempt from poor nutrition. While malnutrition is not an overt national problem, it is endemic in special population groups and requires strenuous public education efforts coupled with economic or food aid where feasible. Obesity has become a major 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 deficiencies such as the anemia of iron deficiency which still persists in a significant segment of the population.

Faced with this challenge, 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. To further research on this critical problem, the Institute has established an Obesity Center at St. Luke's Hospital, affiliated with Columbia University's College of Physicians and Surgeons, New York City, for the multidisciplinary investigation of this condition.

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 normal growth and development, and the consequences and correction of their deficiencies.

The study of nutrition continues with the enthusiasm and urgency 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 revealed the extensive need for research in chronic nutritional disorders.

Scope of Research

The research grants program of the NIAMDD is divided into two categories - 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; the 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 concerns the 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).

RESEARCH ACCOMPLISHMENTS

Treatment of Uremic Osteodystrophy with 1,25-Dihydroxycholecalciferol

NIAMDD grantees have shown that patients with uremic osteodystrophy (bone demineralization in chronic kidney disease) respond to small quantities of the vitamin D metabolite, 1,25-dihydroxycholecalciferol (1,25-DHCC), with beneficial changes noted in the altered calcium state and in skeletal pathologic findings.

Vitamin D is converted in the liver to 25-hydroxy vitamin D_3 and then by the kidney to its highly active, hormonal form, 1,25-dihydroxy vitamin D_3 (1,25-DHCC). Patients with severe kidney disease lose the capacity to make the second conversion from the single hydroxy to the most active dihydroxy form. Short-term oral administration of 1,25-DHCC to patients with advanced renal failure improves calcium and phosphorus balance, enhances intestinal calcium absorption, and corrects or improves hypocalcemia (subnormal blood calcium level). Its effects on the skeletal lesions of uremic osteodystrophy, however, had not been previously known.

The present collaborative study by investigators Drs. Anthony Norman, University of California, Riverside; David Baylink, University of Washington, Seattle; and Jenifer Jowsey, Mayo Foundation, describes the effects of 1,25-DHCC on skeletal abnormalities and parathyroid function in patients with advanced renal failure. Administration of small quantities of the hormone markedly reversed hyperparathyroid manifestations and improved the previously prominent osteodystrophy.

Promising findings noted by the researchers included increased serum calcium levels in all subjects, reduction in loss of bone surface in four patients with osteomalacia, and improved calcification in two. The need for more extensive trials with 1,25-DHCC for the treatment of uremic osteodystrophy is now clearly indicated.

The Effect of 5,6-Trans Vitamin D_3 in Uremia

Recent research by Institute grantees has demonstrated that short-term oral administration of a new vitamin D_3 analog--5,6-trans vitamin D_3--corrects calcium malabsorption in severely uremic patients. This discovery holds promise for use in treating hypocalcemia (subnormal blood calcium level) and consequent secondary hyperparathyroidism and osteodystrophy associated with chronic kidney disease.

Calcium malabsorption in chronic renal disease has been attributed in part to the affected kidneys' inability to convert the vitamin D_3 metabolite, 25-hydroxy vitamin D_3, to its most active form--1,25-dihydroxy vitamin D_3. Although administration of the latter metabolite has been found to correct such malabsorption (see above), it is expensive and cumbersome to synthesize, and to date it has not been available in large enough quantities for large-scale studies on routine treatment of patients.

Attention is now directed to a recently synthesized analog of vitamin D_3, 5,6-trans vitamin D_3, which has been reported to stimulate calcium absorption in uremic subjects. Studies by Drs. Hector DeLuca of the University of Wisconsin, and Saulo Klahr and associates of Washington University, St. Louis, have shown that short-term administration of 5,6-trans D_3 normalizes intestinal calcium absorption in patients with advanced renal disease. The findings strongly suggest that this analog may be beneficial in the treatment of hypocalcemia in patients with renal failure.

Gamma-Tocopherol in Human Vitamin E Nutrition

It has been customary to assess vitamin E activity of the human diet solely on its content of alpha-tocopherol, the most potent vitamin E compound. Recent research by NIAMDD scientists, however, has demonstrated the presence of considerably more gamma-tocopherol than alpha-tocopherol in our food supply. To consider only the alpha compound in calculating the vitamin E activity of food would thus lead to a significant underestimation of this activity.

In animal studies to assess the nutritional importance of the gamma compound, Drs. John G. Bieri and R. Poukka Evarts found that it is now the predominant tocopherol in the U.S. food supply, that it is nearly 10 percent as active as alpha-tocopherol, and that it provides 20 percent of the vitamin E activity in American diets. This stems primarily from the substantial replacement, over the past 20 years, of animal fats (butter and lard) by fats from vegetable oils, particularly soybean, which are high in gamma-tocopherol content.

Studies with rats by NIAMDD investigators in the Institute's Bethesda, Md., laboratories showed that gamma-tocopherol was absorbed from the intestine almost as effectively as the alpha compound, with the former disappearing more quickly from the circulation. In various tissues, ratios of gamma- to alpha-tocopherol, however, varied widely. Plasma and liver had the lowest ratio; spleen and adipose tissue, the highest. In the current calculations of vitamin E activity, either total tocopherols or only the alpha compound in the blood is determined. Since the investigations have shown that plasma is not representative of most other tissues with respect to gamma-tocopherol, a new approach to estimating total vitamin E status in man may be warranted.

Vitamin C - Fact and Fallacies

Vitamin C (ascorbic acid) made its debut into controlled clinical trials in 1747 when James Lind experimented with daily rations of lime juice to determine the value of citrus fruit in the prevention and cure of scurvy aboard ships of the British Navy. Since its nautical beginnings, vitamin C has gained wide recognition--and controversy--for its role in maintaining health. An overview of current research on the vitamin has revealed several significant findings.

The ingestion of large doses (200 mg. or more) of vitamin C has become a popular home remedy to prevent or lessen the severity and duration of the common cold. Although the findings of numerous studies on this subject are unconvincing and inconclusive, scientists do know that the body uses only the amount of ascorbic acid it needs and excretes the rest in the urine. Since the body retains only a small part of massive doses administered, it appears, therefore, that ingestion of such large amounts of C is a waste of time and money.

Other research has lent strong evidence to the fact that the use of very large quantities of C over long periods of time may be harmful. NIH-supported investigators have noted that some persons may be particularly prone to develop kidney stones, nausea, abdominal cramps, or diarrhea. Also, because the body excretes excess vitamin C, its presence in the urine makes accurate testing for diabetes very difficult at best, since it gives a false indication of urine sugar levels.

Other questions about the safety of very high doses of ascorbic acid include its possible adverse affect on fertility and the fetus, interference with treatments of patients whose urine must be kept alkaline, and the possibility of problems in treating persons on anticoagulant therapy. Additional human studies are necessary to clarify these relationships and to determine their clinical importance.

Recent reports from grantee Drs. Victor Herbert and Elizabeth Jacobs further demonstrate that high doses of vitamin C destroy substantial amounts of the vitamin B_{12} supplied by the diet. The Columbia University investigators conclude that daily ingestion of 0.5 gram or more without regular evaluation of B_{12} levels is unwise and may result in vitamin B_{12} deficiency anemia (pernicious anemia).

The recommended daily allowance of vitamin C is set at 45 to 60 mg. daily for women and men respectively; 40 to 55 mg. for children, and 60 mg. for women during pregnancy and nursing. These amounts, it should be noted, may be obtained from the many sources of vitamin C in a balanced diet. Vegetables and fruits--especially the citrus fruits--provide the greatest amounts.

Until more evidence is available about the possible risks as well as the advantages of large doses of vitamin C, it is reasonable to assume that ascorbic acid in amounts specified as the recommended daily allowance will be sufficient to prevent disease and maintain health.

Repeated Weight Fluctuation Enhances Gallstone Risk in Obesity

Research conducted by Drs. Lynn J. Bennion and Scott M. Grundy of the National Institute of Arthritis, Metabolism, and Digestive Diseases in the Institute's Clinical Research Section at the Indian Health Service Hospital, Phoenix, has shown that obese individuals who are subject to gallstones are even more susceptible during a period of weight reduction. Such persons should, therefore, avoid alternately losing and regaining weight.

It is well-known that the obese tend to have gallstones more frequently than lean persons, and that maintenance of normal weight diminishes the risk of developing such accretions. Recent investigations have linked cholesterol gallstone formation to liver secretion of bile that is supersaturated with cholesterol (lithogenic bile). The specific relationship, however, between obesity and bile lithogenicity had not been previously explored.

Studies of gallbladder bile from obese patients now reveal that bile lithogenicity is consistently increased in the obese state, and increased even further during weight loss. Once weight is stabilized at a lower level, however, bile is consistently less lithogenic. Thus, the obese person who alternately loses and regains weight and does so frequently throughout life may intensify his risk of developing gallstones.

No Advantage Found in "High-Low" Diets

Recent research by NIAMDD grantee Dr. D.M. Hegsted and associates at the Harvard School of Public Health demonstrates that when equal numbers of calories are provided, the loss of body fat is not appreciably influenced by large differences in the proportions of carbohydrate, fat and protein in the diet.

Reducing diets low in carbohydrate and high in protein and fat have been repeatedly recommended to the public in the popular press. According to the American Medical Association's Council on Food and Nutrition, this type of diet was first recommended over 100 years ago. Very little experimental evidence is available, however, with either animals or man to support or refute the claims which have been made. Such evidence as is available shows no advantage for such diets.

In the Boston studies, obese rats were given equal calorie intakes while feeding them different diets which varied widely in their respective contents of protein, fat and carbohydrate. Although the high protein regimens resulted in a modest increase in the proportion of body protein, no statistically significant differences in the loss of overall body fat could be demonstrated. The investigators concluded that such a dietary program is of no advantage as a reducing diet when compared to other diets on an equal calorie basis.

Parenteral Feeding: Structural and Hormonal Changes in the Gut

In recent years, intravenous alimentation has been increasingly used to feed seriously ill patients for prolonged periods. Some patients permanently depend on this mode of "alimentation." Yet there has been relatively little study on the effects of the regularly occurring presence of food in the gut on gastrointestinal structure and function and what results from the exclusion of food as in parenteral feeding.

Institute grantee Dr. Leonard R. Johnson and associates of the University of Texas report that intravenous feeding is associated with decreases in gastrin levels (a hormone generated primarily in the stomach which stimulates the secretion there of acid and digestive juices), disaccharidase activity, and the weights of the oxyntic gland or acid secreting areas of the stomach, pancreas and small intestine. These changes can be largely prevented, however, if the deficient hormone, gastrin, is administered. Although these alterations were noted in animals, humans fed parenterally could develop similar changes.

The body weight of rats fed intravenously for three weeks increased by 22 percent, but the weights of the oxyntic gland areas of the stomach, pancreas, and small intestine decreased significantly. Similarly, gastrin levels decreased to one-thirtieth of control levels, and activities of the different disaccharidase enzymes were only a fraction of normal. No similar changes occurred in rats fed by mouth an equicaloric diet.

The researchers subsequently compared rats fed orally with those fed parenterally either a liquid diet alone, or a liquid diet plus pentagastrin or histamine. Only pentagastrin prevented the previously observed changes in gastrointestinal tissues and enzyme activity.

The scientists conclude that oral ingestion of food is necessary to maintain the structural integrity of certain tissues of the gastrointestinal tract, and that maintenance of normal tissue stores of gastrin apparently depends on stimuli provided by this food and its presence in the gut. In addition, gastrin appears to be necessary to maintain proper structure and function of the gut.

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 the Public Law 480 Foreign Currency Program utilizing U.S.-owned local currencies derived from the sale of American surplus agricultural commodities in developing countries. Less than half 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 such 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 this research are two-fold: it may stimulate emergence to self-sufficiency from mere subsistence in Southeast Asian and other developing countries, and may also add knowledge of normal nutrition and nutritional deficiencies that will benefit the U.S. population.

By providing scientific know-how for effective use 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 Southeast Asia and other nations in the Pacific area. In 1975, the U.S. Malnutrition Panel completed its second five-year program of activities with significant progress noted in stimulating and supporting research in line with its objectives, which encompass the following priorities.

1. Determination of the effects of malnutrition on mental development, learning, behavior, physical capability and performance.

2. Studies of the health significance and methods of preventing nutritional anemia.

3. Influence of environment and host factors on nutritional requirements for health in Asian countries.

4. Investigation of the interactions of malnutrition and infection, with special emphasis on the mechanisms responsible.

These priorities include the fundamental problems that have long been a concern but recently have assumed even greater significance with the prospect of a world food crisis. The Panel's program is increasingly relevant to the developing countries in which malnutrition becomes more widespread, and to the populations at nutritional risk in developed countries where economic factors and food availability affect nutritional status and health.

Progress in Priority Areas

Research supported by the U.S.-Japan Cooperative Program has revealed vital data on amino acid and protein requirements, intestinal malabsorption in malnutrition, and the effects of tropical climates on nitrogen metabolism--findings which have expanded our understanding of some of the many host and environmental factors that affect nutritional requirements. New concepts have also been formulated on the interrelationships of nutrition and infection with accumulating evidence on their importance to cell-mediated immunity, metabolic deficiencies, and permanent consequences for physical growth and development.

In related research, the mechanisms involving interactions of nutrition and anemia have been explored, showing iron deficiency as the leading causative factor. This finding has directed attention toward research on the possible deleterious effects of iron deficiency on physical and mental performance as well as toward studies of appropriate means of preventing it. Similarly, studies on the molecular and clinical mechanisms of any possible impairment of mental development, learning and behavior by malnutrition have resulted in 1) a better understanding of the related metabolism of RNA, DNA, and polyamines; 2) development of the technology of stimulation and measurement of the electrophysiological parameters studied; and 3) better understanding of individual as well as collective influences of nutrient deficiencies and environmental stimulation on intellectual capability and performance.

Achievements of some of the projects sponsored by the U.S. Malnutrition Panel in the various priority areas during the past year are listed below.

Studies were conducted by Dr. Adolpho Chavez at the Mexican National Institute of Nutrition with two groups of 17 and 19 mother-child units. The groups, divided into food-supplemented and non-supplemented categories, were traced from pregnancy to the child's fifth year of age.

Comparison between the two groups has demonstrated significant differences in the behavior of the children as well as in their interaction with their families. While the supplemented children exhibited normal social behavior patterns, the non-supplemented group were much less active, interacted less vigorously with their parents, and evidenced retardation in neurological and verbal development.

Studies, from birth, of children in a Guatemalan village have contributed to a better understanding of the relationship between malnutrition and infections. These investigations, conducted by staff at the Institute of Nutrition of Central America and Panama (INCAP), demonstrated the direct association between frequency of infections and impaired growth and development; the relationship between nutritional status and frequency of diarrheal and respiratory infections; and the role of infections during pregnancy on birth weight, and subsequent survival and growth. The results emphasized the importance of environmental and personal hygiene in preventing the spread of diarrheal disease.

The effects of high environmental temperatures on nitrogen loss have been elucidated in the course of studies of the nutritional requirements of young Chinese in Taipei by Dr. P. C. Huang of Taiwan. Apparently, as skin nitrogen loss increases during periods of high temperature, there is a compensatory decrease in urinary nitrogen loss and therefore obligatory nitrogen losses in the same individual vary with the season.

The research activities of Malnutrition and Anemia Research Institute at Chiang Mai, Thailand, have expanded from the initial studies in anemia. Using carefully designed protocols, and carrying out the studies in a metabolic unit, the investigators have shown that protein deficiency per se is a major contributor to the anemia of the severely malnourished infant (along with calorie, vitamin, and mineral deficiencies) through its effects on erythropoietin metabolism and thereby red blood cell formation.

These studies are representative of the multidisciplinary projects currently underway. While the consequences of severe malnutrition are now well recognized throughout the world as major public health problems, the degree to which these effects impair metabolic, physical and mental capabilities continue to be major research challenges. It is abundantly clear that the successful therapeutic and prophylactic solutions for these problems do not lie simply in making food available, but require complex programs that must include cultural, biological, agricultural, economic, and other considerations.

U.S.-Japan Programs

The Malnutrition Panel's priority areas reflect concern for these various dimensions of malnutrition and indicate its commitment to the development of new projects that will expand the knowledge base. In addition to focusing the attention of the scientific community on these problems, the Panel is exploring each area in depth with a comprehensive evaluation of available information, identification of gaps in knowledge, and competent research in order to meet these needs. Practical aspects of nutritional improvement are also included in the array of studies sponsored by this U.S.-Japan Cooperative Program, as illustrated by the next item.

Rice with Increased Protein Content

Ordinary commercial rice lacks sufficient protein for the normal growth and development of infants and children maintained on a predominantly rice diet, and does not protect the adult population from serious protein undernutrition. At the International Rice Research Institute in the Philippines, a project is underway to improve the protein content of commercial rice from about 7% to about 10%. Such an upgrading of a basic staple would introduce an automatic and sweeping nutritional improvement in all the populations for whom this one crop represents the nutritional mainstay, including many segments of the population of the United States: Mexican-Americans, Puerto Ricans, Southern Negroes, among whom pockets of malnutrition have recently been discovered.

During earlier work in this project, new high-protein varieties of rice had been developed at the International Rice Research Institute. The project involves nutritional testing of these new varieties which includes laboratory analysis followed by biologic testing in animals and man. In preliminary experiments with young adults in the United States, this new rice has been shown to sustain a positive nitrogen balance in college students on a special diet of rice as the only source of protein; in contrast, students who were given a rice containing 7% protein developed a negative nitrogen balance.

Verification of the nutritional advantage of replacing rice containing the conventional protein content with a high-protein rice lies in its inclusion in rice-based weaning foods for actively growing preschool children. Last year, a study was completed of the effect that replacing rice of average protein content with rice of higher protein content in a rice-fish weaning diet had on nitrogen retention of Filipino male children, 1.5 to 2 years old. This study showed that nitrogen retention in milligrams per kilogram of body weight increased progressively with an increase in the protein content of the rice variety used in different rice-fish weaning diets. This is the first direct and successful demonstration of the nutritional advantage of increasing the protein content of rice and confirms earlier experiments which yielded similar results in laboratory animals.

Nutrition Education

Advances brought about through research achieve their full potential only when such knowledge is disseminated to and used by appropriate segments of the lay and professional communities. To aid in achieving this goal, several projects, initiated this year within the Institute, form the basis of an effective, nationwide, public education effort.

A collaborative project with the National Education Association (NEA) provided for distribution of the latest revised edition of the Institute booklet "Facts About Nutrition" to approximately 63,000 junior and senior high school libraries across the country. This publication gives a detailed yet simple explanation of proper dietary practice for all age groups from infancy to the aged. Its availability was also the subject of spot television and radio announcements prepared through NIH's "Health Spots for Radio" programs which reach 2,000 radio and 700 TV stations nationwide.

In related projects, the Institute prepared for general dissemination articles addressing frequently-asked questions on nutrition. Published through NIH's "Search for Health" column series, the articles are made available to over 500 weekly newspapers across the country. In addition, two new publications, "Facts About Obesity" and "Research Advances in Nutrition" have been prepared for distribution to the general public.

A booklet entitled "Diet Guide for Patients on Chronic Dialysis" was printed this year by the Institute's Artificial Kidney-Chronic Uremia Program for dissemination to appropriate audiences. Written in simple, non-technical language, the booklet provides an easy-to-follow guide for dialysis patients (who must be on a special diet for as long as they are on dialysis), which enables them to convert their dietary prescription into a healthful, attractive menu. The booklet has proved so popular that within six months of its first printing, it had been distributed, by request, to 6,000 of the currently 20,000 dialysis patients in the United States.

The enthusiasm with which this initial program was received has confirmed public education as an integral part of our expanding nutrition research effort.

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 rapidly becoming less dependent on ill-defined symptoms or on the subjective judgment of the examining physician.

The investigations this past year have proved productive and illustrate the continuing need to extend our knowledge base of human nutrition. Such knowledge provides the basis for progress in the prevention and treatment of many nutrition-related chronic disease conditions. The Institute is anticipating even more significant advances in these research efforts in the coming years.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Amounts Available for Obligation

	1976 Appropriation	1977
Appropriation	$175,172,000	$180,837,000
Legislation Pending	4,344,000	---
Subtotal, appropriations	179,516,000	180,837,000
Comparative transfer from:		
"Office of Director" for Standard level user charges	285,000	---
Total obligations	179,801,000	180,837,000

National Institute of Arthritis, Metabolism, and Digestive Diseases

Budget Mechanism

	1976 Appropriation			1977		
	Number	FTE 1/	Amount	Number	FTE 1/	Amount
Grants						
Regular						
Non-competing...	1,476		$96,762,000	1,554		$101,980,000
Competing.....	284		16,093,000	154		9,341,000
New.....	189		10,728,000	102		6,227,000
Supplemental....	(95)		1,200,000	(95)		1,200,000
Subtotal.....	1,949		124,783,000	1,810		118,748,000
Special						
Multi-disciplinary centers.....			4,048,000			5,437,000
Research career programs.....		168	4,368,000		148	4,090,000
Scientific evaluation....			372,000			496,000
Subtotal.....		168	8,788,000		148	10,023,000
Total Grants.....			133,571,000			128,771,000
Fellowships						
Non-competing.....	172	239	4,174,000	152	240	4,383,000
New.....			---	51	84	1,500,000
Subtotal.....	172	239	4,174,000	203	324	5,883,000
Training Grants						
Non-competing.....		21	170,000			---
Intramural Research and Other Direct Operations.....			32,252,000			35,064,000
Research and Development Contracts.....	94		8,792,000	110		10,162,000
Program Management..			557,000			588,000
Standard Level User Charges.....			285,000			369,000
Total.....			179,801,000			180,837,000

1/ Full-time equivalents.

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DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1977 JUSTIFICATION

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
(Amounts in thousands)

Program	Research Grants				Training Programs		Intramural Research and Other Direct Operations	Research and Development Contracts	Program Management	Total
	Regular Program		Specials							
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Arthritis, Bone and Skin Diseases.....	$19,463	$5,690	---	$690	$28	$879		$815		$27,565
2. Diabetes, Endocrinology and Metabolism....	37,472	10,562	$1,885	2,340	16	1,507		823		54,605
3. Digestive Diseases and Nutrition.....	19,685	6,282	2,163	1,191	86	935		2,120		32,462
4. Kidney Disease, Urology and Hematology....	20,142	5,487	---	519	40	853		5,034		32,075
5. Intramural Research and Other Direct Operations....							$32,537			32,537
6. Program Management....									$557	557
Total Obligations..	96,762	28,021	4,048	4,740	170	4,174	32,537	8,792	557	179,801

DHEW - National Institutes of Health

CROSSWALK - 1977 COLUMN 1977 JUSTIFICATION

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES
(Amounts in thousands)

Program	Research Grants				Training Programs		Intramural Research and Other Direct Operations	Research and Development Contracts	Program Management	Total
	Regular Program		Specials							
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Arthritis, Bone and Skin Diseases.....	$20,219	$3,324	---	$646	---	$1,387		$1,070		$26,646
2. Diabetes, Endocrinology and Metabolism....	39,507	6,497	$2,736	2,338	---	1,679		917		53,674
3. Digestive Diseases and Nutrition.....	21,305	3,503	2,701	1,116	---	1,153		2,575		32,353
4. Kidney Disease, Urology and Hematology....	20,949	3,444	---	486	---	1,664		5,600		32,143
5. Intramural Research and Other Direct Operations....							$35,433			35,433
6. Program Management....									$588	588
Total Obligations..	101,980	16,768	5,437	4,586	---	5,883	35,433	10,162	588	180,837

Summary of Changes

1976 Appropriation	$179,801,000
1977 Estimated Obligations	180,837,000
Net change	+1,036,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Within-grade pay increases	---	$8,661,000	---	+$260,000
2. Annualization of 1976 pay raise costs in 1977	---	710,000	---	+229,000
3. Bureau of employee compensation (BEC) rate increase	---	22,000	---	+3,000
4. Federal Telecommunications System (FTS) rate increases	---	20,000	---	+4,000
5. Postage rate increase	---	102,000	---	+65,000
6. Travel per diem rate increase	---	98,000	---	+73,000
7. Standard Level User Charge increase	---	285,000	---	+84,000
8. Payment to NIH management fund	---	10,579,000	---	+1,168,000
9. Increased program analysis and general expense account	---	1,089,000	---	+603,000
10. Increased assessment for primary review of research grants	---	372,000	---	+124,000
Subtotal	---	---	---	+2,613,000
B. Program:				
1. Net increase of 78 noncompeting continuation grants awarded in prior years	---	96,762,000	---	+5,218,000
2. Support of 256 new and competing grants in 1977	---	26,821,000	---	+15,568,000
3. Five additional multi-disciplinary centers in diabetes and digestive diseases	---	4,048,000	---	+1,389,000
4. Support of 94 additional fellows	---	4,174,000	---	+1,709,000
5. Incremental cost of intramural research supplies, materials and services	---	7,196,000	---	+475,000
6. Support of 16 additional research and development contracts	---	8,792,000	---	+1,370,000
Subtotal	---	---	---	+25,729,000
Total increases	---	---	---	+28,342,000

Summary of Changes--continued

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Decreases:				
A. Built-in:				
1. One less day of pay in 1977...	381	$8,661,000	---	-$37,000
Subtotal.....	---	---	---	-37,000
B. Program:				
1. Completion or conversion to noncompeting status of 473 new and renewal research grants awarded in 1976.....	---	26,821,000	---	-26,821,000
2. Eleven fewer research career awards than in 1976.....	---	4,368,000	---	-278,000
3. Phase out of training grants program.....	---	170,000	---	-170,000
4. Reduction of positions.....	588	---	-28	---
Subtotal.....	---	---	---	-27,269,000
Total decreases.....	---	---	---	-27,306,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
156	Arthritis, Bone and Skin Diseases.....	$24,027,000	$27,565,000	$26,646,000	-$919,000
159	Diabetes, Endocrinology and Metabolism.....	48,187,000	54,605,000	53,674,000	-931,000
163	Digestive Diseases and Nutrition.....	27,910,000	32,462,000	32,353,000	-109,000
166	Kidney Disease, Urology and Hematology.....	28,537,000	32,075,000	32,143,000	+68,000
169	Intramural Research and Other Direct Operations.....	32,625,000	32,252,000	35,064,000	+2,812,000
	Positions.....	540	568	540	-28
173	Program Management...	557,000	557,000	588,000	+31,000
	Positions.....	20	20	20	---
	Standard Level User Charges.....	285,000	285,000	369,000	+84,000
	Total obligations.....	162,128,000	179,801,000	180,837,000	+1,036,000
	Total positions....	560	588	560	-28

Obligations by Object

	1976 Appropriation	1977 Estimate	Increase or Decrease
Total number of permanent positions	588	560	-28
Full-time equivalent of all other positions	56	60	+4
Average number of all employees	612	615	+3
Personnel compensation:			
Permanent positions	$11,116,000	$11,476,000	+$360,000
Positions other than permanent	992,000	1,028,000	+36,000
Other personnel compensation	290,000	294,000	+4,000
Subtotal, personnel compensation	12,398,000	12,798,000	+400,000
Personnel benefits	1,699,000	1,735,000	+36,000
Travel and transportation of persons	467,000	360,000	-107,000
Transportation of things	65,000	70,000	+5,000
Rent, communications and utilities	470,000	540,000	+70,000
Printing and reproduction	220,000	230,000	+10,000
Other services	4,254,000	4,716,000	+462,000
Payment to NIH management fund	10,864,000	12,116,000	+1,252,000
Project contracts	8,792,000	10,162,000	+1,370,000
Supplies and materials	2,131,000	2,656,000	+525,000
Equipment	526,000	800,000	+274,000
Grants, subsidies and contributions	137,915,000	134,654,000	-3,261,000
Total obligations by object	179,801,000	180,837,000	+1,036,000

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1976 House Report	
1. "Some of the increased funds provided in the bill should be used for the purpose of implementing the Arthritis Act and the Diabetes Act."	1. Of the funds in the final appropriation bill $340,000 was set aside for the National Arthritis Commission and $220,000 for the National Diabetes Commission. An increase of $2,747,000 was provided for research in arthritis as was an increase of $1,239,000 for research in diabetes.
1976 Senate Report	
1. "The Committee...expects to receive budget recommendations in this area, [sic] research support of academic rheumatologists, as soon as possible from the Director of NIAMDD."	1. The requested report has been forwarded.
2. "The Committee recommends NIAMDD set aside $700,000 of its fiscal year 1976 appropriation for the work of the (Arthritis) Commission."	2. (See House Report above).
3. "Of the additional funds provided, $300,000 shall be for the National Diabetes Commission."	3. (See House Report above).

Authorizing Legislation

Legislation	1977 Authorized	1977 Appropriation requested
Public Health Service Act Section 301--Research and Investigation, in general	Indefinite	$174,954,000
Title IV, Part D--National Institute on Arthritis, Metabolism, and Digestive Diseases	Indefinite	
Title IV, Part D--Diabetes Research and Training Centers	$20,000,000	1/
Title IV, Part D--Arthritis Screening, Detection, Prevention and Referral Demonstration Projects; and Data Bank	4,000,000	1/
Title IV, Part D--Comprehensive Arthritis Centers	15,000,000	1/
National Diabetes Mellitus Research and Education Act Section 3--National Commission on Diabetes	1,000,000	2/
National Arthritis Act of 1974 Section 3--National Commission on Arthritis and Related Musculoskeletal Diseases	2,000,000	2/
Title IV, Part I--National Research Service Awards Act	Pending	5,883,000 3/

1/ Requests pursuant to these authorizations are dependant on the final reports of the National Diabetes Commission and the National Arthritis Commission respectively.

2/ No requirement for support of these commissions is anticipated for 1977.

3/ Authorization expired June 30, 1975; extension legislation is proposed.

National Institute of Arthritis, Metabolism, and Digestive Diseases

Year	Budget Estimate to Congress	Comparable House Allowance	Senate Allowance	Appropriation
1966	119,203,000	121,203,000	123,203,000	123,203,000
1967	130,193,000	133,972,000	135,972,000	135,972,000
1968	144,239,000	144,239,000	147,489,000	144,239,000
1969	152,003,000	141,572,000	147,572,000	144,173,000
1970	137,953,000	137,953,000	155,285,000	146,904,000
1971	132,437,000	138,624,000	140,624,000	138,624,000
1972	135,879,000	148,650,000	164,075,000	153,449,000
1973	132,142,000	158,592,000	173,276,000	158,592,000 1/
1974	134,003,000	156,289,000	163,395,000	153,956,000 2/
1975	153,181,000	162,427,000 3/	178,220,000	173,265,000
1976	148,694,000	174,257,000 4/	177,257,000 4/	
Items not Considered	---	(4,344,000)	(4,344,000)	
1977	180,837,000			

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 as authorized by PL 93-192.

3/ Excludes amount for contracts not considered by the House due to lacking authorization.

4/ Excludes amount for training not considered by House or Senate due to lacking authorization.

The figures presented in this Table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of General Research Support Grants is no longer the function of this Institute. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes.

National Institute of Arthritis, Metabolism, and Digestive Diseases

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Actual 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	173,972,000 4/	176,972,000 4/	
Items not Considered	---	(4,344,000)	(4,344,000)	
1977	180,837,000			

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 as authorized by PL 93-192.

3/ Excludes amount for contracts not considered by House due to lacking authorization.

4/ Excludes amount for training not considered by House or Senate due to lacking authorization.

Justification

National Institute of Arthritis, Metabolism, and Digestive Diseases

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Arthritis, Bone and Skin Diseases.....	$24,027,000	$27,565,000	$26,646,000	-$919,000
Diabetes, Endocrinology and Metabolism.....	48,187,000	54,605,000	53,674,000	-931,000
Digestive Diseases and Nutrition.....	27,910,000	32,462,000	32,353,000	-109,000
Kidney Disease, Urology and Hematology.....	28,537,000	32,075,000	32,143,000	+68,000
Intramural Research and Other Direct Operations.....	32,910,000	32,537,000	35,433,000	+2,896,000
Positions.....	540	568	540	-28
Program Management.....	557,000	557,000	588,000	+31,000
Positions.....	20	20	20	---
Total.....	162,128,000	179,801,000	180,837,000	+1,036,000
Positions.	560	588	560	-28

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 93% of the funds in these program categories are used for grants and 7% 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 473 applicants in 1976 and 256 in 1977 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 1,949 individual research projects in 1976 and estimates it will support a total of 1,810 projects in 1977.

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 1976 approximately 94 contracts will be awarded for a one year period, although future support may be planned. In 1977 approximately 110 contracts will be supported.

Previously supported programs for research training have been phased out and in their place a new program was 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 support 239 fellows in 1976 and 333 in 1977.

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.

Arthritis, Bone and Skin Diseases

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Arthritis.....	---	$12,976,000	---	$14,919,000	---	$14,287,000	---	-$632,000
Bone Diseases....	---	7,015,000	---	8,100,000	---	7,777,000	---	-323,000
Skin Diseases....	---	4,036,000	---	4,546,000	---	4,582,000	---	+36,000
Total.....	---	24,027,000	---	27,565,000	---	26,646,000	---	-919,000
Budget Mechanism:								
Research Grants								
Regular:								
Noncompeting...	297	19,463,000	297	19,463,000	308	20,219,000	+11	+756,000
Competing.....	34	2,247,000	87	5,690,000	51	3,324,000	-36	-2,366,000
Subtotal.....	331	21,710,000	384	25,153,000	359	23,543,000	-25	-1,610,000
Special.....	---	565,000	---	690,000	---	646,000	---	-44,000
Subtotal.....	331	22,275,000	384	25,843,000	359	24,189,000	-25	-1,654,000
Fellowships 1/...	54	954,000	49	879,000	77	1,387,000	+28	+508,000
Training Grants 1/.....	3	28,000	3	28,000	---	---	-3	-28,000
Research & Development Contracts.....	5	770,000	5	815,000	6	1,070,000	+1	+255,000
Total.....	---	24,027,000	---	27,565,000	---	26,646,000	---	-919,000

1/ Numbers are full-time equivalents.

Arthritis, Bone and Skin Diseases

Arthritis and Related Diseases

The major aims of the arthritis program are to define fully the diseases which fall into this category in terms of their respective causes and complications, and to find methods for optimal treatment or prevention. This mission is fraught with great difficulty because of the diversity of the individual disorders which make up "arthritis" and the rheumatic diseases, and because, as a whole, their individual causes are as yet not known.

In rheumatoid arthritis, the mechanism at work in causing the 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, and future research will be directed in this area.

Research will also be concentrated on the search for more effective drugs to ameliorate the associated symptoms.

Until recently, synovectomy, surgical removal of the thickening synovial tissue, was generally used only in advanced cases, but evidence has shown that synovectomy at an early stage can lead to regrowth, in the same joint, of healthy tissue. Usually this procedure results in reduced inflammation in the joint, with accompanying relief from pain. Further research is needed to determine which patients are likely to benefit from synovectomy and what the long-term effects of the surgery would be on the progression of rheumatoid arthritis.

Studies on other forms of arthritis such as systemic lupus erythematosus and gout will also be pursued.

The Institute will of course, within budgetary constraints, attempt to carry out as many as possible of the recommendations of the National Commission on Arthritis and Related Musculoskeletal Diseases, and will continue joint US-USSR programs in collaboration with Soviet rheumatologists in arthritis research.

Bone Diseases (Orthopedics)

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. The most severe cases may require reconstructive orthopedic surgery to correct deformed joints, or total replacement of nonfunctioning joints with artificial prostheses.

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 goal of orthopedics research. Successful transplants of 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. Many of these efforts involving connective tissues and cartilage will be directed toward a better understanding of biochemical structure, ultra-structure, genetic factors, and enzymology of these tissues, as well as to the process of tissue-skeletal repair.

Another promising area of orthopedic research is the enhancement of bone fracture healing through local application of a mild electric current. Several Institute grantees have recently demonstrated success in this area both in adults with previously non-healing fractures and in children with congenital non-union of bones.

Skin Diseases

Disorders of the skin include psoriasis, a disfiguring disease which numbers as its victims some four million Americans. The total number of persons afflicted with psoriasis and other dermatologic problems is large, and personal suffering is of great magnitude. The other major dermatologic diseases are eczematous and eczematoid dermatitis; acne vulgaris, a disease of sebaceous glands; fungal and bacterial infections, warts, herpes simplex, and other viral infections; disorders of the subcutaneous tissues with scleroderma and lupus erythematosus being the best known of the collagen diseases of skin; burns and their subsequent scars; abnormalities of pigment regulation causing vitiligo ("piebaldness") and also one of man's deadliest cancers -- melanoma. Pemphigus is a chronic

blistering disorder of the skin and, like malignant melanoma, is ultimately fatal.

The Institute's dermatology program is the only extramural program within the NIH that has a specific responsibility for supporting research on disorders of the skin and its appendages including hair, nails, sebaceous glands, and sweat glands.

In psoriasis, therapeutic management has been generally unsatisfactory and certain drugs with a therapeutic potential have, also, unfortunately, caused serious side effects. Recently, however, 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. This method of management ("photochemotherapy") of psoriasis however, has been tried for only a short time and it will now be subjected to intensive, controlled investigation for long-term effectiveness and for determination of its safety and freedom from undesirable side effects.

Institute-supported studies will continue to screen and develop chemotherapy agents for the topical treatment of severe psoriasis. A limited number of cytotoxic (anti-cancer) drugs will be tested on the skin of psoriatic patients for potential therapeutic effectiveness.

Diabetes, Endocrinology and Metabolism

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Diabetes.....	---	$11,137,000	---	$12,329,000	---	$13,350,000	---	+$1,021,000
Endocrinology....	---	16,387,000	---	18,516,000	---	18,038,000	---	-478,000
Metabolism.....	---	20,663,000	---	23,760,000	---	22,286,000	---	-1,474,000
Total.....	---	48,187,000	---	54,605,000	---	53,674,000	---	-931,000
Budget Mechanism:								
Research Grants								
Regular:								
Noncompeting...	572	37,472,000	572	37,472,000	602	39,507,000	+30	+2,035,000
Competing.....	67	4,337,000	161	10,562,000	99	6,497,000	-62	-4,065,000
Subtotal.....	639	41,809,000	733	48,034,000	701	46,004,000	-32	-2,030,000
Special.....	---	3,875,000	---	4,225,000	---	5,074,000	---	+849,000
Subtotal.....	639	45,684,000	733	52,259,000	701	51,078,000	-32	-1,181,000
Fellowships 1/...	98	1,667,000	90	1,507,000	100	1,679,000	+10	+172,000
Training Grants 1/.....	2	16,000	2	16,000	---	---	-2	-16,000
Research & Development Contracts.....	7	820,000	7	823,000	8	917,000	+1	+94,000
Total.....	---	48,187,000	---	54,605,000	---	53,674,000	---	-931,000

1/ Numbers are full-time equivalents.

Diabetes, Endocrinology and Metabolism

Diabetes

A complicated disease for which there is no known cure, diabetes ranks sixth on the list of diseases causing death in the United States. Diabetes has been known for some time to be, in part, a hereditary disorder. As a result of the body's inability to metabolize carbohydrates normally, the diabetic is unable to convert carbohydrates properly into the stored form, glycogen, or to utilize them properly for the energy required for normal body functions. The carbohydrates, in the form of glucose, accumulate in the blood and overflow into the urine. As the disease progresses, abnormal carbohydrate metabolism becomes associated with a noticeable derangement in the metabolism of fats and proteins, and with changes in the cardiovascular system and in the small blood vessels of the body.

During the next fiscal year, Institute efforts will continue to focus on attempts to define the disease in terms of its causes and the many complications associated with it, and to find methods of prevention. In this regard, the Institute will also attempt to carry out as many as possible of the recommendations to the Congress

of the the National Commission on Diabetes within the budgetary resources available.udgetary

Basic knowledge about diabetes still to be discovered includes the mechanism of action of insulin, a clearer understanding of the intricate details of carbohydrate and fat metabolism in the disease, and determination of the precise nature of the blood vessel abnormalities which underlie major complications of the disorder. The Institute is also concerned with exploring ways to suppress development of complications of diabetes which include enhanced atherosclerosis and consequent coronary heart disease, nerve damage, kidney failure and blindness.

The Institute plans to launch a contract-supported program to extend current efforts to develop a mechanical insulin-supply system, an "artificial pancreas" which can maintain normal blood sugar levels in human diabetic patients. Other important research which will receive scrutiny during the next fiscal year will be centered around the recent discovery of somatostatin, a hormone which inhibits the release of glucagon and other hormones. Glucagon is believed to be an important agent in causing the sugar level to become markedly elevated and in antagonizing the natural actions of insulin. Since somatostatin suppresses glucagon, scientists are anxious to determine its exact role in influencing the course of diabetes and hence its potential for therapeutic use.

The Institute will also continue to support several Diabetes-Endocrinology Research Centers throughout the United States. Center grants will be limited to institutions where there is ongoing research in diabetes, and will be used to strengthen and to permit further development of these efforts. These centers will provide core resources and services at an institution where a broad and substantial volume of excellent diabetes research already exists.

Endocrinology and Endocrine Disorders

Endocrinology concerns itself 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. Thus, research in the field of endocrinology is considered one of the most important areas of Institute concern.

For many years endocrinologists were concerned with the clinical conditions resulting from under or over-production of the endocrine glands. In recent years, the importance of the hormones as control factors in the metabolism, growth and reproduction of the whole body, and particularly of the individual cells, has become more and more evident.

The Institute supports basic and clinical research on: the normal and abnormal functioning of the endocrine glands; the structure, function, and mechanism of action of the hormones produced; the effects of the hormones on various processes in the body; and the factors which contribute to the control of the effects of the endocrine system (e.g., hypothalamic secretions, prostaglandins, cyclic AMP, and others).

Most clinical symptoms of the dysfunction of endocrine glands are well-known and in most cases can be alleviated; however, not well-understood is the basis of hormonal control at the cellular level. This is important to all branches of medicine since the

hormones markedly affect cellular function and the metabolism of nutrients and other cell-components. It has become apparent that the hormones act at the cellular level through a complicated system involving hormone receptors at the cell membrane, "second" intracellular messengers such as cyclic AMP, and by activation of intracellular enzyme systems.

Because of the importance of knowing the precise mechanism of hormonal action on cells and tissues, NIAMDD will support many basic studies on hormone action as well as more clinically oriented investigations of the diseases caused by hormonal imbalance. The clinical studies will include investigations of such abnormalities as: osteoporosis, pituitary dwarfism, acromegaly, thyroid disorders, adrenal dysfunction, and others.

Osteoporosis is a condition in which there is too little bone tissue, and hence the bones tend to fracture as the result of minor trauma or strain. It may be caused by postmenopausal hormonal insufficiency, malfunction of the adrenals or pituitary gland, prolonged dietary calcium deficiency or skeletal disuse, and by combinations of two or more of these factors. It is quite common in postmenopausal women, who account for the majority of the millions of osteoporosis patients. Efforts will be made to clarify the nature of osteoporosis and to seek better treatment for it.

In recent years investigators have determined the chemical structure of the pituitary gland hormones, thyroid stimulating hormone (TSH) and luteinizing hormone (LH). Now, investigators have determined the amino acid sequence of follicle stimulating hormone (FSH), the only pituitary gland glycoprotein hormone whose structure was still unknown. Further research on FSH may lead to a better understanding of fertility drugs.

Probably one of the most important advances in the field of endocrinology has been the 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.

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.

The Institute has contracted for the operation of the National Pituitary Agency (NPA) to increase and improve the collection of human pituitary glands and to provide for the distribution of purified human growth hormone (HGH) to qualified research scientists with the aid of a knowledgeable 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 pituitary fractions to selected investigators for research purposes. At present, HGH can only be administered to patients 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.

An evaluation of the National Pituitary Agency by a select group of experts chosen by the National Academy of Sciences-National Research Council from various biomedical disciplines has concluded that the NPA has fulfilled the "important purpose for which it was created," and has resulted in "very large cost benefits to the scientific community, and thus to the NIH."

Metabolism and Other Metabolic Diseases

The Institute supports basic and clinical research on all the complex chemical changes which take place in body tissues, and on the cellular level, which represent the biochemical basis for all life processes from minute-to-minute energy conversion through growth and aging. This 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, phenylketonuria, Wilson's disease, galactosemia, the various glycogen storage diseases, congenital nonhemolytic jaundice, and many others.

Many of these and other metabolic diseases are known to result from an enzyme deficiency. Of the therapeutic approaches to diseases due to hereditary enzyme deficiency, induction or transfer of enzyme activity is in many ways the most attractive and will be examined further in the year to come.

Digestive Diseases and Nutrition

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Digestive Diseases.....	---	$20,402,000	---	$23,286,000	---	$23,569,000	---	+$283,000
Nutrition.....	---	7,508,000	---	9,176,000	---	8,784,000	---	-392,000
Total	---	27,910,000	---	32,462,000	---	32,353,000	---	-109,000
Budget Mechanism:								
Research Grants								
Regular:								
Noncompeting...	300	19,685,000	300	19,685,000	325	21,305,000	+25	+1,620,000
Competing.....	34	2,212,000	96	6,282,000	53	3,503,000	-43	-2,779,000
Subtotal.....	334	21,897,000	396	25,967,000	378	24,808,000	-18	-1,159,000
Special.....	---	3,129,000	---	3,354,000	---	3,817,000	---	+463,000
Subtotal.....	334	25,026,000	396	29,321,000	378	28,625,000	-18	-696,000
Fellowships 1/...	57	988,000	54	935,000	66	1,153,000	+12	+218,000
Training Grants 1/.....	11	86,000	11	86,000	---	---	-11	-86,000
Research & Development Contracts.....	8	1,810,000	10	2,120,000	16	2,575,000	+6	+455,000
Total.....	---	27,910,000	---	32,462,000	---	32,353,000	---	-109,000

1/ Numbers are full-time equivalents.

Digestive Diseases and Nutrition

A broad array of recurring ailments of the digestive tract is undergoing investigation; foremost among these are: peptic ulcer, ulcerative colitis, regional ileitis (Crohn's disease), and such malabsorption disorders as celiac disease. In addition to the numerous maladies of the gastrointestinal tract itself are the equally debilitating diseases which afflict related organs, such as the gallbladder, pancreas and liver.

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 outpatient treatment and countless social and emotional problems. Some diseases such as Crohn's disease are of a chronic nature. Many patients are afflicted for years and may have to undergo extensive and repeated treatments and surgery.

Among the many research studies which will continue to be supported during Fiscal Year 1977 are investigations into the possibility of dissolving gallstones through the oral administration of a specific bile salt to obviate the need for recourse to surgery.

Another 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.

Through 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 prevention and to improvements in its diagnosis and medical and surgical treatment.

The Institute will also plan 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 prevention diagnosis, and treatment of these disorders.

As part of the Institute's efforts to intensify program efforts in the area of digestive diseases, a newly begun collaborative research project, the National Cooperative Crohn's Disease Study, will continue. This study is designed to examine the efficacy of several commonly used regimens in the treatment of regional ileitis (an inflammatory disease of the bowel), which has devastating effects on its patients, young adults in particular, causing prolonged periods of hospitalization and frequently leading to abdominal operations involving resection or removal of portions of the intestine.

The study, involving eight university medical centers, is a controlled, randomized clinical evaluation of the efficacy of three currently used drugs, prednisone, azulfidine and azathioprine, compared to a placebo, to determine the relative effectiveness of these agents. The study will initially examine each drug's effectiveness in preventing intensification of the disease, and the second phase will determine the effect of each drug in preventing recurrence of the disease.

Nutrition

The Institute's nutrition program will continue to focus on those aspects of basic and clinical nutritional sciences which have particular relevance to improvement of human health and longevity. In the main, these are concerned with advancement of knowledge concerning the nutritional role of vitamins, trace minerals and elements, proteins and amino acids, fats, fatty acids and carbohydrates, and their relationships to normal and disordered states of metabolism. In certain of these areas, encouraging and important advances have been made during the past fiscal year by investigators whose research has been supported in large part by Institute funds.

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).

Among nutrition research studies during Fiscal Year 1977 will be those regarding the destruction of vitamin B contained in food by large doses of vitamin C (of the type advocated in some quarters for prevention and treatment of the common cold). 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 percent 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 lipids and lipid metabolism, effects of fasting and periodicity of eating, neural and other factors influencing appetite, endocrine dysfunctions and hereditary factors.

Kidney Disease, Urology and Hematology

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Kidney Disease and Urology	---	$18,860,000	---	$21,306,000	---	$21,609,000	---	+$303,000
Hematology	---	9,677,000	---	10,769,000	---	10,534,000	---	-235,000
Total	---	28,537,000	---	32,075,000	---	32,143,000	---	+68,000
Budget Mechanism:								
Research Grants								
Regular:								
Noncompeting	307	20,142,000	307	20,142,000	319	20,949,000	+12	+807,000
Competing	35	2,325,000	129	5,487,000	53	3,444,000	-76	-2,043,000
Subtotal	342	22,467,000	436	25,629,000	372	24,393,000	-64	-1,236,000
Special	---	419,000	---	519,000	---	486,000	---	-33,000
Subtotal	342	22,886,000	436	26,148,000	372	24,879,000	-64	-1,269,000
Fellowships 1/	57	1,061,000	46	853,000	90	1,664,000	+44	+811,000
Training Grants 1/	5	40,000	5	40,000	---	---	-5	-40,000
Research & Development Contracts	67	4,550,000	72	5,034,000	80	5,600,000	+8	+566,000
Total	---	28,537,000	---	32,075,000	---	32,143,000	---	+68,000

1/ Numbers are full-time equivalents.

Kidney Diseases, Urology and Hematology

Kidney Disease

In an attempt to improve the understanding of the workings of the kidney and related urinary tract organs, the Institute supports a broad program, which includes studies of the basic mechanisms of kidney function and the urinary tract in both health and disease. Some of the major kidney/urologic diseases studied in the program include pyelonephritis, glomerulonephritis and other immunologic diseases of the kidney, the nephrotic syndrome, polycystic disease, urolithiasis (kidney stones), benign prostatic hypertrophy, urinary tract infections, renal hypertension, and end-stage kidney disease (uremia). The precise etiological bases of several of these diseases are still unknown but infections, genetic defects, hypertension and systemic blood vessel disease, aberrations of immune mechanisms, and chemical and mechanical injury are all considered to contribute.

Irreversible end-stage kidney disease or uremia is recognized from a composite of signs and symptoms caused by the kidney's inability to remove the body's protein-derived metabolic wastes and other dietary elements and to regulate its internal chemistry. Although two dramatic therapeutic approaches to end-stage kidney disease, namely

chronic hemodialysis and kidney transplantation, have been developed to cope with fatal end-stage kidney disease, current knowledge does not foster primary prevention of chronic kidney disease with the exception of prevention of infections of the urinary tract and surgical correction of congenital abnormalities of the collecting and excretory system.

Although a wide range of investigations of the kidney have increased our ability to cope with the problem of kidney failure, research efforts in Fiscal Year 1977 must and will continue towards achieving prevention and control of immunologic glomerular kidney disease, hypertensive kidney disease, and chronic infections. In addition, studies will continue in the treatment of early kidney failure, which should reduce and postpone markedly the need for dialysis or transplantation and the attendent human and economic costs. The new fiscal year will see continued research to evaluate the effectiveness of varied combinations and doses of drugs used to prevent the rejection of grafted kidneys, the main problem in transplantation.

Graft rejection occurs because the body's internal defense system attacks foreign tissues and organs just as it attacks invaders such as viruses and bacteria. Although tissue typing and subsequent rational matching of donor kidneys and transplant recipients has helped to reduce this problem to some extent, physicians must use immunosuppressive drugs as an ongoing additional control for the duraction of the life of the patient. These drugs are toxic, and tend to weaken the body's immunity to infectious microorganisms as well as to the transplanted foreign tissues. Use of the drugs must be carefully regulated if the patient is to retain his transplant without suffering the possible adverse effects of a weakened immunological system.

One such promising investigation will study animals that have kidney transplants by treating them with various combinations and dosages of new and currently used immunosuppressive agents to determine which combination therapy best prevents transplant rejection with few, if any, side effects. The condition of each animal will be monitored, through weekly laboratory tests of its blood and urine and periodic renal biopsies, to evaluate the effects of the drugs on both the health of the animal and the viability of the transplant.

Artificial Kidney Program

In Fiscal Year 1977, priority will be assigned to studies related to the pathophysiology of uremia. Emphasis will be on the complications of long-term dialysis -- the anemia of uremia, peripheral neuropathy, the hypertension and hyperlipidemia characteristic of long-term dialysis which is implicated in the heart and vascular disease deaths (the predominant cause of death in long-term dialysis patients). Emphasis will also be placed on development of new methodology which will permit reduction of the total number of hours devoted weekly to dialysis and on determination of what constitutes adequate dialysis treatment. There will be a determined effort for improvement of clinical dialysis methodology, with emphasis on "custom-tailored" individualized treatment schedules, prevention of the rather common clinical complications, thus--more effective cost control.

Considerable research effort on abnormal metabolites of uremia has not yet achieved a level of full understanding of this complex problem. Significant progress, however, has occurred in the

understanding of uremic bone disease, now permitting control of this complication of dialysis in a large number of cases. Studies will continue to be devoted to the mechanisms which underlie uremic anemia, neurological malfunctions, and other complications of uremia such as accellerated atherosclerotic blood vessel degeneration.

One of the most important activities underway is the quantitation of dialysis therapy now under study using different experimental membranes or altered dialysis protocols and the latest newly developed dialysis hardware with the objective of defining quantitatively the extent of dialysis treatment required for each type of patients. Such research is now possible because of the availability of a wide range of membranes, dialyzers dialysis protocols, and new, rational research hypotheses.

Continued support is planned for research on novel methods of treatment of uremia which promise to have advantages not now available through conventional hemodialysis.

Hematology

Hematology represents an indispensable part of the Institute's grant-supported research. The sum total of Americans afflicted with the disabling and fatal disorders of the blood, excluding circulatory problems, but including the anemias, and blood clotting disorders such as hemophilia, is considerable. In Fiscal Year 1977, research will cover a wide range of studies which may be characterized as either working towards control of blood disease or utilizing blood as a biological tool to study other biomedical problems.

A number of specific areas identified as targets for the extramural research program are genetic disorders of hemoglobin and its production such as Cooley's anemia and other thalassemias; the non-genetic anemias and disorders of blood cell production; enzymatic and metabolic defects of blood cells; and immunology of organ transplantation and of autoimmune hematologic disease. The hypochromic anemias, a broad category of blood disorders characterized by deficient hemoglobin production, also constitutes a wide health problem, including, as it does, iron deficiency anemia.

The often fatal end-result of repeated blood transfusion, the only known therapy for Cooley's anemia victims, is the accumulation of iron deposits in vital organs. Development of a safe, effective oral chelating agent, to remove this excess iron would end the major objection to transfusion therapy, which is otherwise generally well-tolerated. Chemists now consider that such an agent could be developed with present technology, and this pursuit will remain a goal of Institute-supported researchers in the next fiscal year.

While there is a steady growth of knowledge about the blood diseases, further basic research is needed to understand better the various relevant disease processes and to permit development of effective therapy. Recent advances in the isolation and purification of certain blood fractions essential for the normal clotting process ("Factor VIII") now make possible effective stoppage of bleeding in patients with hemophilia and even permit major surgery after prophylactic administration of purified antihemophilic factor.

Intramural Research and Other Direct Operations

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Intramural Research.....	$26,405,000	$26,032,000	$28,388,000	+$2,356,000
Positions.....	454	468	454	-14
Other Direct Operations..	6,505,000	6,505,000	7,045,000	+540,000
Positions..	86	100	86	-14
Total.....	32,910,000	32,537,000	35,433,000	+2,896,000
Positions..	540	568	540	-28

Intramural Laboratory and Clinical Research

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 and to pursue studies on diagnosis, treatment, and presention in specific diseases. 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.

Arthritis and Rheumatism

In addition to studying the possibility that rheumatoid arthritis is the result of chronic inflammation probably triggered by an abnormal immune reaction, Institute scientists will be evaluating methods to remove rheumatoid granulation tissue (pannus) from affected joint areas in selected patients. Preliminary research has indicated that surgical removal of this tissue will prevent the progressive destruction of cartilage, bone, and periarticular supporting structures that is characteristic of rheumatoid arthritis.

Like rheumatoid arthritis, systemic lupus erythematosus (SLE) is another connective tissue disorder. It develops in about 50,000 new patients each year, most often affecting people in the 20-40 year age group, particularly young women.

Although the cause of SLE is not known, much evidence points, as in the case of rheumatoid arthritis, to a disorder of the body's immune mechanism which may or may not be tied to a previous infectious process. The disease can appear as a result of hypersensitivity to certain drugs, and this phenomenon is among those being studied by Institute researchers at the NIH Clinical Center. Patients are also under investigation there in a study involving the immunosuppressive

drugs cyclophosphamide and azathioprine in the treatment of certain of the complications of SLE.

Diabetes and Other Metabolic Diseases

Institute diabetes research in the coming fiscal year will concentrate on studies to understand the basic impairment of insulin activity, a complete knowledge of which would uncover some of the riddles now surrounding diabetes. Research will focus 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 multiple essential effects on cellular processes, and may permit development of rational and effective treatments for diabetic patients.

Institute researchers will also continue clinical studies of cystic fibrosis, with additional related 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 result. 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.

The Southwestern Field Studies Section will continue its epidemiological investigation of diabetes mellitus among Indians of the Southwestern United States, and in particular, the Pima Indians of Arizona who have a diabetes incidence about ten times that of the rest of the population in the United States. Various factors, including hereditary, environmental, dietary, and anthropological aspects that may have a bearing on the frequency and severity of this disease, are and will continue to be investigated. Selected findings are being contrasted with similar studies performed on other populations with different characteristics and environments.

Endocrinology

Endocrinology, the study of the internal glandular secretions of the body and the glands which discharge these secretions, is an immense biomedical field. Its involvement in many diseases cannot be underestimated, as it directly pertains to important life functions, such as growth, metabolism, and reproduction.

Among Institute intramural research projects planned for the next fiscal year, investigators will be studying parathyroid disorders and hormone-conditioned metabolic bone diseases. The recent development of a highly sensitive radioimmunoassay for parathyroid hormone is expected to improve diagnostic accuracy for hypo- or hyperparathyroid states and allow measurement of rates of secretion of the hormone which exerts a regulatory influence on bone mineral metabolism. Patients with hypercalcemia, hypophosphatemia, nephrocalcinosis, nephrolithiasis, or other manifestations of

hyperparathyroidism will be examined for the therapeutic effects of calcium or EDTA infusions or dietary phosphate on the secretion of parathyroid hormone.

Digestive Diseases

Intramural digestive disease research will continue to cover clinical and laboratory investigations to determine abnormalities in structure and function of the esophagus, stomach, small and large intestines, pancreas and liver, and research on certain hereditary metabolic diseases. Work will be directed at an understanding of human digestive tract disease and its treatment in terms of underlying derangements in the body's metabolism and physiology.

An exciting new concept of treating cholesterol gallstones medically rather than surgically has shown considerable promise. The oral administration of a natural bile acid, chendeoxycholic acid, has resulted in the diminution or disappearance of cholesterol gallstones in most of the subjects tested so far. During this coming year the Digestive Diseases Branch will participate in therapeutic trials of this medical approach to the dissolution of gallstones.

In addition, primary biliary cirrhosis and vinyl chloride associated liver disease will be investigated. The latter disorder involves individuals with evidence of liver disease having a history of occupational exposure to vinyl chloride. Other research will cover the causes and manifestations of intestinal malabsorption.

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.

Institute clinical research in blood disease this coming fiscal year will stress, among other studies, the biochemistry of blood coagulation with particular reference to the development of better forms of therapy for various congential and acquired hemorrhagic diseases. Such disorders as hemophilia A or B, von Willebrand's disease, hemophiloid conditions such as Factor VII deficiency, circulating anticoagulants, afibrinogenemia, fibrinolysis, as well as obscure, undiagnosed bleeding disorders, will be studied. New approaches to therapy of acute and chronic idiopathic thrombocytopenic purpura (ITP) and the thrombocytopenia of lupus erythematosis (a generalized connective tissue disease) will also be evaluated.

Nearly all of the increase for this subactivity in this budget request is 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. In addition, an increase of $475,000 will provide an incremental increase to cover the rising cost of supplies, materials and services in order to maintain the current level of research effort.

Other Direct Operations

Nearly two-thirds of the resources of this subactivity 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 information relevant to all transactions.

The other major function under this subactivity is the review, management and negotiation of research and development contracts of the categorical program areas, the largest contract program being the Artificial Kidney/Chronic Uremia Program which is developing more effective, less costly methods of treatment of end-stage kidney disease.

The entire increase for this subactivity 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.

Program Management

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Program Management.....	$557,000	$557,000	$588,000	+$31,000
Positions.....	20	20	20	---

This activity provides support for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, property control and travel audit and control, which are most efficiently performed as centralized functions. This staff, which continues to absorb new responsibilities and reporting functions such as required under the Freedom of Information Act and the manpower productivity measurement program, has remained at the same level over the past decade.

The entire budget increase requested for this activity is required for mandatory items including annualization of the 1976 pay raise, within-grade pay increases and increased postage charges.

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)

1976 Appropriation			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$26,658,000	Indefinite	---	$25,259,000
---	907,000	Pending	---	1,387,000

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 1976: In 1976, 384 research grants, 49 fellowships, 1 training grant, and 5 contracts were awarded. Of the research grants awarded, 297 were noncompeting continuations of previous awards and 87 were new and competing continuations. All of the fellowships and training grants were noncompeting continuations.

Objectives for 1977: The estimate for 1977 provides for 359 research grants, 77 fellowships, and 6 research and development contracts. Of the research grants, 308 will be noncompeting continuations and 51 will be new or competing renewal awards. Of the fellowships, 51 will be for noncompeting continuations and 16 will be new awards. The phase-out of the training grant program has been completed and no future awards will be made.

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)

1976 Appropriation			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$53,082,000	Indefinite	---	$51,995,000
---	1,523,000	Pending	---	1,679,000

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 1976: In 1976, 733 research grants, 90 fellowships, 1 training grant, and 7 contracts were awarded. Of the research grants awarded, 572 were noncompeting continuations of previous awards and 161 were new and competing continuations. All of the fellowships and training grants were noncompeting continuations.

Objectives for 1977: The estimate for 1977 provides for 701 research grants, 100 fellowships, and 8 research and development contracts. Of the research grants, 602 will be noncompeting continuations and 99 will be new or competing renewal awards. Of the fellowships, 79 will be for noncompeting continuations and 21 will be new awards. The phase-out of the training grant program has been completed and no future awards will be made.

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)

1976 Appropriation			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$31,441,000	Indefinite	---	$31,200,000
---	1,021,000	Pending	---	1,153,000

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 1976: In 1976, 396 research grants, 54 fellowships, 3 training grants, and 10 contracts were awarded. Of the research grants awarded, 300 were noncompeting continuations of previous awards and 96 were new and competing continuations. All of the fellowships and training grants were noncompeting continuations.

Objectives for 1977: The estimate for 1977 provides for 378 research grants, 66 fellowships, and 16 research and development contracts. Of the research grants, 325 will be noncompeting continuations and 53 will be new or competing renewal awards. Of the fellowships, 42 will be for noncompeting continuations and 14 will be new awards. The phase-out of the training grant program has been completed and no future awards will be made.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Kidney Disease, Urology and Hematology (Public Health Service Act Title IV Parts D and I)

1976 Appropriation			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$31,182,000	Indefinite	---	$30,479,000
---	893,000	Pending	---	1,664,000

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 1976: In 1976, 436 research grants, 46 fellowships, 2 training grants, and 72 contracts were awarded. Of the research grants awarded, 307 were noncompeting continuations of previous awards and 129 were new and competing continuations. All of the fellowships and training grants were noncompeting continuations.

Objectives for 1977: The estimate for 1977 provides for 372 research grants, 90 fellowships, and 80 research and development contracts. Of the research grants, 319 will be noncompeting continuations and 53 will be new or competing renewal awards. Of the fellowships, 71 will be for noncompeting continuations and 19 will be new awards. The phase-out of the training grant program has been completed and no future awards will be made.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Intramural Research and Other Direct Operations (Public Health Service Act Title IV Parts D and I)

1976 Appropriation			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
568	$32,537,000	Indefinite	540	$35,433,000

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.

Nearly two-thirds of the resources of this subactivity 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 application 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 organization; continuous surveillance of scientific activities and progress; and recording and reporting of fiscal and scientific information relevant to all transactions.

The other major function under the subactivity is the review, management and negotiation of research and development contracts of the categorical program areas, the largest contract program being the Artificial Kidney/Chronic Uremia Program which is developing more effective, less costly methods of treatment of end-stage kidney disease.

Objectives for 1977: Nearly all of the increase for this subactivity in the budget request is 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 building and grounds, custodial services, communications, and transportation. In addition, an increase of $475,000 will provide an incremental increase to cover the rising cost of supplies, materials and services in order to maintain the current level of research effort.

NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases

Program Purpose and Accomplishments

Activity: Program Management (Public Health Service Act Title IV Parts D and I)

1976 Appropriation			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
20	$557,000	Indefinite	20	$588,000

Purpose: This activity provides support for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, property control and travel audit and control, which are most efficiently performed as centralized functions. This staff, which continues to absorb new responsibilities and reporting functions such as required under the Freedom of Information Act and the manpower productivity measurement program, has remained at the same level over the past decade.

Objectives for 1977: The entire budget increase requested for this activity is required for mandatory items including annualization of the 1976 pay raise, within-grade pay increases and increased postage charges.

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Appropriation	Transition Quarter
Arthritis, Bone and Skin Diseases.....	$27,565,000	$6,788,000
Diabetes, Endocrinology and Metabolism.....	54,605,000	13,910,000
Digestive Diseases and Nutrition.....	32,462,000	8,308,000
Kidney Diseases, Urology and Hematology.....	32,075,000	8,086,000
Intramural Research and Other Direct Operations.....	32,537,000	7,863,000
Program Management.....	557,000	147,000
Total.....	179,801,000	45,102,000

Explanation

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 appropriation. Estimates for individual programs were based on historical accounting data for the same period in previous years.

WEDNESDAY, FEBRUARY 25, 1976.

NATIONAL INSTITUTE OF DENTAL RESEARCH

DR. DAVID B. SCOTT, DIRECTOR
DR. CLAIR L. GARDNER, ASSOCIATE DIRECTOR, EXTRAMURAL PROGRAMS, NATIONAL INSTITUTE OF DENTAL RESEARCH
DR. JAMES P. CARLOS, ASSOCIATE DIRECTOR, NATIONAL CARIES PROGRAM, NATIONAL INSTITUTE OF DENTAL RESEARCH
MRS. FRANCES H. PETTINATO, ACTING EXECUTIVE OFFICER, NATIONAL INSTITUTE OF DENTAL RESEARCH

Mr. NATCHER. Dr. Scott, we are delighted to have you appear before the committee. With your permission, if we could place your statement in its entirety in the record and then proceed with our questions, it would be a help to the committee.

Dr. SCOTT. Yes, sir.

[The statement follows:]

Mr. Chairman and members of the committee, as you know, this is my first appearance before this committee, and it is a privilege to testify on behalf of the National Institute of Dental Research.

I had served the Institute for a long period as laboratory chief, and after an absence of 10 years, I am proud to be associated with NIDR again. From my previous vantage point in the scientific and academic community, I can say that the achievements of NIDR scientists are acclaimed throughout the world. The time limitations of this statement preclude any detailed discussion of the tremendous advances, important not only to dentistry but biomedical research in general, that have come from the Institute's studies in biochemistry, microbiology, immunology, virology, and biological structure. I am committed to this continuing record of excellence by our intramural staff as well as the contributions of a growing body of outstanding extramurally supported investigators.

I am also happy to be coming back at a time that the Institute is finally able to begin some demonstration programs in the prevention of dental caries. Just as soon as the state of the art permits us to do so in our other fields of study, I am committed to undertake such programs to hasten the application of preventive and therapeutic techniques.

DENTAL CARIES

Institute scientists played a major role in the establishment of a scientific base for our highly targeted national caries program. This program is designed to identify and develop cost-effective preventive methods and to rapidly bring them to the point of widespread public use. It encompasses a wide range of studies of topical fluorides, tooth sealants, oral antimicrobial drugs, dietary sugar substitutes, enzymes to remove plaque from the teeth, anticaries vaccines, and the technology to deliver these methods once they are perfected. At the same time, the program continues more basic research efforts to better clarify the complex etiology of caries.

Newly acquired information on the mechanism of fluoride action has led to the development of a regimen of weekly fluoride mouth rinsing in school classrooms, a simple, inexpensive preventive technique. From the results of previous clinical trials, reductions in the incidence of tooth decay of up to 40 percent have been shown. Approximately 75,000 children in 17 nonfluoridated communities are now involved in a program to demonstrate the method.

Unfortunately, fluorides are not highly effective against caries which develops in the pits and fissures of the chewing surfaces of teeth. A method to seal these

vulnerable areas with a plastic adhesive was developed by a grantee. In 1975 we completed field trials with this sealant in over 3,000 children, and we have established its safety and efficacy. The incidence of new decay is eliminated as long as the tooth surfaces remain sealed. The sealant has been retained by over 60 percent of the teeth for 2 years or longer. We have also shown that it is possible to apply this material with properly trained auxiliary personnel, thereby reducing costs.

Since the bacteria which cause caries are at least partly identified, the use of antimicrobial compounds is a logical preventive approach. The national caries program has established a collaborative program with the pharmaceutical industry to subject potentially useful compounds to intensive screening tests in animals and humans. From over 100 compounds tested to date, several are considered promising enough to warrant further tests, and one of them is now ready for controlled clinical trials.

PERIODONTAL DISEASE

Our research in periodontal disease builds on previous findings by institute scientists and grantees that only bacteria of specific types can cause the disease and that much of the tissue destruction which results in the loss of teeth may be brought about by immune inflammatory mechanisms within the body. Significant progress continues to be made in delineating the complex tissue destructive immune responses that occur as a result of interactions among certain white cells.

An investigation during the past year has shown that white cells called B-lymphocytes can produce a substance that kills fibroblast cells, which synthesize the collagen fibers that constitute the structural base of the periodontal tissues. Further studies showed that specimens of diseased human gums produced 25 to 35 percent less collagen—fibrous tissue—than specimens of healthy tissues. At the same time, other studies proved that the collagen-destroying enzyme called collagenase exists in human gingiva in an inactive form, and can be activated by substances obtained from inflammatory lymphocytes. Thus, the total loss of fibrous tissue observed in periodontal disease is probably due to both decreased production and increased destruction.

The role of bacterial endotoxins, which earlier were shown to seep into the gingival tissues from the periodontal plaque and trigger inflammation and destruction of tissues, has now been enlarged. During the past year investigators found that endotoxin also becomes adsorbed to tooth roots exposed by periodontal disease. When human tooth roots with adsorbed endotoxin were placed in tissue cultures with gingival tissue cells, the cells did not attach to the root surfaces. However, when the endotoxin was removed from the roots, cells did attach. It is likely that this substance may also prevent reattachment in a similar manner in human disease, and this possibility will be explored.

An ongoing clinical study has shown that treatment of advanced cases of severe periodontal disease with debridement combined with the antibiotic tetracycline, 1 gram per day for 21 days every 6 months, has prevented further damage for 3 years. These findings further strengthen the concept of employing antibiotics as an adjunct in periodontal treatment and spur the search for more specific drugs. Efforts also center on developing an effective delivery system for drugs now available.

I am pleased to report also that NIDR conducted a comprehensive evaluation of its entire periodontal disease program this past year. The primary purpose of the evaluation was to assure a productive and properly balanced research effort with regard to the causes of the disease, its destructive action, therapy, and prevention.

NUTRITION

Nutrition research was first emphasized by NIDR approximately 2½ years ago. Findings to date, primarily in animal studies, show that nutritional deficiencies both in early life and later contribute to increased caries, enamel defects, disturbances of salivary gland function, and increased permeability of the mucous membrane to bacterial endotoxin. Recent studies also show that lack of vitamin C causes the formation of a small molecular defect in collagen which makes it unable to form the ropelike structure that gives strength to fibrous tissue. The Institute will continue to encourage grant-supported research in this important area.

In related studies on oral sensation and perception. Institute scientists have shown that newborn infants can distinguish certain tastes, such as the sweetness

of sugar. In other mammals, preference for sweet substances has been shown to follow early exposure. This research suggests that early taste experience contributes significantly to generating the subsequent dietary habits in our culture.

VIRAL INFECTIONS

A major focus of our studies of viral infections is the recurrent herpes simplex virus, which affects a large part of the population. One type of this virus causes troublesome fever blisters as well as eye infections, and another type of herpes is responsible for genital infections. Last year we reported that this virus, when latent, can be isolated from the sensory ganglia of the nervous system of mice. More recently, our scientists have shown that the herpes simplex virus also resides in autonomic ganglia. Since the autonomic system controls all involuntary functions, this finding may have implications for not only oral diseases but other diseases of the gastrointestinal tract including peptic ulcers and ulcerative colitis. Efforts still continue to develop a vaccine.

As an outgrowth of studies of diseases of both the salivary gland and pancreas, our scientists have found a genetic factor in the development of virus-induced diabetes in mice. The virus induces the diseases by attacking pancreatic beta cells of susceptible strains of mice. Further work may clarify whether diabetes in man is of viral origin and whether there are hereditary implications. As you know, the National Diabetes Mellitus Research and Education Act of 1974 charges the Dental Institute, together with six other institutes at NIH, with the responsibility of developing a coordinated research program in diabetes.

CRANIOFACIAL ANOMALIES

A major research effort is being made to identify the causes of craniofacial malformations, with continuing emphasis on cleft lip and palate. While some clefts appear to have an hereditary basis, the interactions of genetic and environmental factors are still not understood. Analytic population studies have indicated possible associations between clefts and prenatal factors such as drugs used to control epileptic seizures by pregnant women. Similar associations with the use of tranquilizers during pregnancy were reported by the Public Health Service's Center for Disease Control in Atlanta, Ga. Laboratory studies of animal models have also demonstrated the relationship between these drugs and an increase in the incidence of clefts. These animal studies are continuing to unfold the mechanism of how clefts are caused by these agents. There is also promise of great progress in the newly developing application of molecular biology in causal studies of cleft formation. Cleft lip and palate have now been associated with over 100 craniofacial syndromes.

As a result of animal studies to improve surgical procedures, it may soon be possible to avoid the retarded growth of the upper jaw which has often followed conventional cleft palate surgery. These new methods are now ready to be tested in humans.

To combat the problem of malocclusions, we continue to seek greater understanding of normal as well as abnormal craniofacial growth, maturation, and aging. Large pools of data on samples of normal human populations have been accumulated and sorted. Animal and human studies are currently focusing on an interceptive program for malocclusion designed to guide craniofacial growth patterns at an early childhood age. Other recent studies have suggested that since some skull sutures fuse late, it may be possible to effect favorable alterations of facial shape in adults by the application of localized forces.

RESTORATIVE MATERIALS

The basic formulation of all of the composite filling materials on the market, is the result of discoveries made by NIDR-supported research. The composite resins are considerably more durable than previous synthetic materials, and are used for restoring front teeth. However, they do not as yet have sufficient mechanical strength for use on chewing surfaces of molar teeth. A novel class of reinforcing fillers now under study hold promise of greater strength and longevity.

Various material are being studied for their effectiveness as tooth implants. Among them, a bioglass ceramic, vitreous carbon, and titanium are being tested

in baboons. We are greatly encouraged by initial data indicating that tissues adjacent to the implants are similar in some charactersitics to tissue adjacent to natural teeth.

ORAL PAIN CONTROL

The Dental Institute has exercised a strong leadership on the field of pain research. It played a key role in the establishment of the International Association for the Study of Pain and in the organization of the First World Congress on Pain, which was held last September. The Institute was asked to serve as the focal point for continuing work in standardization of the terminology used in the evaluation, diagnosis, and treatment of clinical pain syndromes. In addition, the Institute is conducting and supporting research to achieve a better understanding of pain and associated anxiety and to develop more effective means to control them. Research findings emphasize the importance of psychologic factors in the cause and response to treatment of temporomandibular joint—jaw hinge—pain. It was also found that acetaminophen, a common nonnarcotic pain reliever, is more effective than codeine in providing comfort following dental surgery. The drug allows the patient to function better with fewer side effects than a narcotic.,

DENTAL RESEARCH INSTITUTES

The dental research institutes, now in their ninth year of operation under grant support from NIDR, continue to make gratifying progress. In addition to basic research, the institutes are moving toward the application of new knowledge in clinical investigations. These studies encompass pain control, herpetic infections, periodontal disease, dental caries, and malocclusion, among other problems.

BUDGET REQUEST

In conclusion, Mr. Chairman, the budget request for the National Institute of Dental Research for fiscal year 1977 is $52,207,000. This budget will permit us to continue studies to further clarify the causes, pathogenic effects, mechanisms of action, treatment, and prevention of dental and oral-facial diseases. Emphasis will also continue to be placed on related areas of restorative materials and control of pain. Opportunities for the development of preventive measures, which may be generated by ongoing research, will be promptly pursued. I shall be pleased to try to answer any questions and supply additional information desired for the record.

Mr. NATCHER. Before we proceed, tell us who these people are you have with you.

Dr. SCOTT. Thank you, Mr. Chairman. To my immediate left is our acting executive officer, Mrs. Frances Pettinato. Next to her is Dr. James P. Carlos, associate director for the national caries program, and at the end is Dr. Clair L. Gardner, associate director for extramural programs.

Mr. NATCHER. Thank you.

BUDGET

Doctor, your budget shows an increase of $780,000 for fiscal year 1977. This is not a tremendous increase, but we would like for you to tell us what you plan to do with that.

Dr. SCOTT. The $780,000 is basically a differential that has been brought about by increased cost of operation. And it reflects, as you can see on page 104, various adjustments that had to be made for increased costs. Actually, many were down. There is a slight increase in the caries program, again attributable mostly to the cost of operation. There is very little increase in program substance.

NATIONAL CARIES PROGRAM

Mr. NATCHER. In the statement that you made to the committee you said that one of the objectives of the dental caries program is to identify and develop cost-effective prevention methods and to bring them to widespread public use.

Can you give us some examples of what you have done in this area in the last 2 years, and what you plan to do in fiscal year 1977?

Dr. SCOTT. Yes, sir. The primary thing that is going on now is in connection with what our group feels is a cost-effective technique—the use of a low concentration fluoride rinse. That is now in the demonstration stage in 17 different areas geographically scattered through the United States.

As you know, there was another program on sealants to evaluate their effectiveness. This program has been completed. The data are now in, and if one looks at last year's testimony, or that from the year before, questions were always asked about progress in the program. It is our feeling now that the procedure is not ready for a demonstration process at this point, mainly because of the cost-effective factor. As it turns out, now that the data have been analyzed in the last few months and the papers on the results of the studies have been prepared for publication; the cost-effectiveness may present a problem. It appears that this measure may not have the makings of an especially economic public health procedure to be used by a community that would eventually have to pick up the cost. However, it is extremely effective for usage in the hands of a private practitioner, and that is where we will for the time concentrate our efforts. For the 1977 year, there are also efforts planned or in progress that will be continued relative to certain other prospective agents for the control or prevention of caries. Some studies will be mounted to demonstrate further the effectiveness of mixing a couple of procedures, such as either topically applied fluoride or fluoride rinse, connected with the use of sealants—that sort of progressive study to see what the effectiveness would be.

SEALANTS

Mr. NATCHER. In your statement you said that the Dental Institute completed field trials of a plastic adhesive sealant, and you have established its safety and efficiency. When will this be available to every dentist across the country?

Dr. SCOTT. That is the program I just mentioned, which our staff feels may not be especially cost-effective as a public health measure. It has been available to dentists now for a couple of years I would say, and our best information to this point indicates that it has been fairly slowly adopted by the dentists. The latest figures we have are that about two-thirds of them are not using the technique at this moment. This does not, I believe, reflect necessarily lack of knowledge or retrogressiveness, but it reflects perhaps a caution and a desire to have further information about the measure. The latest information is being spread, and I think you will see an increase in its utilization, especially in the case of children.

Mr. NATCHER. Approximately what is the additional cost now as far as applying the sealant?

Dr. SCOTT. That is a very difficult question to answer because it is a personal matter with the particular practitioner. I can speak best for where I came from in the dental school. Our fee for that was somewhere on the order of $15 for the entire mouth. This reflects, of course, very low recovery in a student training situation, and costs outside could vary tremendously, depending on the conditions, the number of visits that have to be made, the amount of time consumed. I would hesitate to give a figure. The cost is not much less than the student rate cited, however, in the data accumulated for the trials that we have conducted in the field. That is why the feeling is that for usage in public programs, there might be some problems with cost.

XYLITOL

Mr. NATCHER. In your justification material you state that you are planning to initiate the first U.S. trial of xylitol, a noncariogenic dietary substitute. Where do you plan to do this, Doctor, and give us some idea as to how much you plan to spend on this clinical trial.

Dr. SCOTT. The matter of xylitol as a sucrose substitute came up in Finland. Xylitol, as you know, is derived from plant products, birch tree bark, and also from various vegetables. Some very interesting studies came forth out of Finland on this that have been reported over the last year or so. There were six or seven studies all run in tandem, a very heroic effort, and these investigators deserve a lot of credit.

They in essence developed a little factory that obtained the product, this sugar substitute, and then they manufactured foods with it, and also confections and chewing gum and the like, to be used as substitute for sucrose containing substances. They achieved quite a reduction in caries.

Our group here feels xylitol, which incidentally is considered by the FDA as a safe product, should probably be tried. One of the statements they made was that chewing gum with xylitol, a few sticks a day, had a caries retarding or preventive effect. They felt the effect was not only in the common context of reducing consumption of fermentable sugars, but also some other side effect of the xylitol, probably against the microbial flora of the oral cavity. Our group plans to start with that as a jumping-off place, and see whether the notion of the chewing gum as a positive medium for control of disease might be feasible, since it is commonly used, it is acceptable to the public, highly acceptable, and as a matter of fact, tastes very good. We do not know where this will be done yet, because it will be under contract. The RFP will go out and we will see who responds to it. The desire is to have at least 400 to 500 children use the material.

PUBLIC EDUCATION

Mr. NATCHER. Last year Dr. Kreshover told us that there are very little time and resources available in the Institute to engage in a public education campaign. Is this still the situation? As the new Director, are you planning to change this situation any?

Dr. SCOTT. The matter of public education in my mind falls as a problem for the whole Public Health Service. One of the things I

started doing as soon as I got here, was to get together with the other people in the Public Health Service who manage the dental activity—there are four people—one from Health Manpower, one from CDC, Dr. John Greene, chief dental officer, who is an assistant to Dr. Cooper and myself. We have had several conferences to find out where things can best be done. This is very important due to the reorganizations that have taken place. In the 10 years I have been gone there has been considerable reorganization. But our bigger concern is where things may not get done, what may fall in the crack, because there is little or no duplication of effort now among the different parts of the PHS. I think the feeling is developing out of our gatherings that we ought to consider the matter of education as a more or less tripartite effort.

As for the professionals—certainly Health Manpower has the best access to them, as for the public, CDC has programs planned to get to them. We fall more or less in the middle, needing to develop the research information to put out, and also to disseminate some of it both at the professional and at the public level.

In direct answer to your question, our office for dissemination of information at any level you may choose is small and provision has not been made to enlarge it very much. We feel it is doing an excellent job. It is reaching the media, it is getting a great deal of material out.

The public is certainly being reached through our clinical demonstration programs, and by other media demonstrations being put on by the information office.

I do not really know where we can go in this without giving serious consideration to where it subtracts necessary resources from the primary research thrust. It is a bit of a dilemma, because I quite agree that without the dissemination of information our ultimate effectiveness in communication is problematical.

Your direct question was for the public. I think all parts of PHS probably had better take a good look at who can face various missions the best and most effectively.

FEDERAL SUPPORT

Mr. NATCHER. We were told during last year's hearings that the National Institute for Dental Research provided 66 percent of all federally supported dental research. We were also told that no formal mechanisms were established to coordinate your work with the dental research supported by other Federal agencies.

Is this the situation today, or have there been any changes?

Dr. SCOTT. So far as I can tell, the situation is much the same today. But I would alert you to the fact that most all researchers are in communication, and there is no void in the knowledge among people involved in the research on all fronts, as to what is going on.

So far as coordinating activities, this depends, I suppose, on how much overlay there is. And that, of course, we will look at. But as I see it now, I think in the military, they deal with populations to which they have immediate access, and they can do extremely good research that probably we would not be able to do under our own system.

Whether there is any other overlap, I would not know yet. As you are aware, there is a special committee looking at this situation. And we certainly will be interested in their recommendations, too.

PLAQUE

Mr. NATCHER. Doctor, have any of your grantees come up with a chemotherapeutic agent that appears promising as a way to prevent plaque or inhibit bone destruction?

Dr. SCOTT. Well, that is a knotty question. Agents come and go, under test conditions. Plaque, of course, is involved both in caries and in periodontal disease, and bone destruction basically only in periodontal disease. In periodontal disease, the antibiotics look extremely promising. In fact some work within both our intramural and extramural programs is now showing that one can achieve quite a bit of plaque control, and indeed disease control in the periodontal area, by short sequences of tetracycline administered over a 3-week period. That is superimposed on all kinds of highly motivated hygienic procedures administered by the patient himself. The problem now is to find a more specific antibiotic, without using a broad spectrum drug which might be needed for other purposes.

In the field of caries, much the same sort of thing is coming, but more along chemotherapeutic lines, with various offshoots of fluoride compounds, other agents, and some in the line of antibiotics as well.

PERIODONTAL EVALUATION

Mr. NATCHER. If you will, please, submit for the record at this point just a short statement now amplifying a little bit more your opening statement to the committee concerning the evaluation of your periodontal disease research activity. And if you would, give us the results of this study, and just submit that for the record.

Dr. SCOTT. Would you like a comment now?

Mr. NATCHER. Yes; if you would—just a short comment now.

Dr. SCOTT. I think that's all I should give you now, sir, because the report is not officially in my hands. As you would guess, in preparing for this hearing, I could not resist having a preliminary look. But the final meeting on that will be held in about a week, and the document will be in our hands as soon as it is typed up after that.

It looks to me as if what the document will say is basically that this blue ribbon committee was highly satisfied with our general efforts in research intramurally and extramurally toward the problem of periodontal disease. They make an exception, I think, by saying that certain of the grants should be looked at a second time, which is quite understandable. The main thrust of the report, I believe, will say that the efforts along clinical research lines are weak. This, I think I would have said from personal observation, from the outside—both intramurally and extramurally, we do need to strengthen the clinical component of our research activities, and most especially in the periodontal disease area. And I think the final thing it will say is that we are not advanced enough in our knowledge, to a point where we could mount a line item targeted program, such as a national periodontal disease program, a counterpart of the caries program. Those, I think, would be the prime conclusions.

I will be glad to give you the summary statement when the report comes in.

Mr. NATCHER. That will be fine.

[The information follows:]

Ad Hoc Scientific Panel Evaluation of the NIDR Periodontal Disease Research Activity

SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

The panel strongly and unanimously believes that there should continue to be a periodontal disease research program, comprising both extramural and intramural research activities. Without such a program, research on this major public health problem would not be carried out effectively. The present program brings a research focus on periodontal disease and facilitates planning of the total research effort, both basic and applied. It offers the best hope of controlling periodontal disease.

The panel identified many strong features of the NIDR periodontal disease research program. It has yielded a great deal of information on the etiology of periodontal disease, about which much more is now known than for most other diseases. A notable feature of the program has been the immense contributions it has made to the knowledge of connective tissues and to the understanding of immune responses. In these two areas, some of the world's finest and most productive research has been supported by NIDR funds. Other strengths of the program include the high scientific quality of many of the research projects and the fact that it has attracted a number of outstanding scientists of periodontal research.

Two major weaknesses were identified: program imbalance in the relative lack of clinical research and unevenness in scientific quality among the research projects.

Clinical research.—The application of information from basic research to the problems of periodontal disease has been far from optimal. Relatively little clinical research is currently being supported by NIDR. The panel recommends increased emphasis on extramural clinical research and on clinical research within NIDR to supplement the Institute s excellent basic research.

There is an overriding need for clinical studies of the local etiology and the preventive and treatment measures presently available for combating periodontal disease. The panel recommends that the NIDR make an aggressive, sustained effort to expand and strengthen this indispensable part of its researcl effort.

Scientific quality.—The panel assessed and scored all research projects in terms of meeting the program objectives. Four criteria were used: scientific quality, potential to meet the objective, scientific achievement, and special features. The panel assigned scores for scientific quality to all projects and while, in most cases, the scores were very high, approximately 25 percent of the projects did not score as well. While the panel recognizes that some of these lower scores may have been the result of inadequate information and other factors, it recommends that NIDR make a special review of these projects.

The major research area, periodontal microbiology, is receiving inadequate attention and support. The panel believes that, with the recent demonstration of the critical role of microbial plaque in the etiology of gingivitis, increased effort and support in this area is now needed.

Two approaches which would help to promote periodontal research are (1) the encouragement of cooperative ventures, and (2) the provision of training programs:

Cooperation should be encouraged between research workers with specialized and complementary expertise, who are located in different institutions. Existing mechanisms such as program projects and cooperative clinical research grants should be simplified and promoted for this purpose, especially for clinical research projects.

In view of the continuing need for well-trained young researchers to work on periodontal disease, the panel strongly advocates support of training in biomedical disciplines. It is equally important that training programs with flexible support be provided for training in the application of basic research to clinical problems of periodontal disease.

With recent advances in periodontal and biomedical research, the current state of knowledge is such that appropriate expenditure on periodontal research is now likely to produce substantial dividends.

The current annual Federal support for all aspects of periodontal disease, which amounts to less than $11 million, is quite inadequate. The panel recommends that annual Federal support for the NIDR periodontal disease research program should increase over the next 3 years to at least $15 million (in 1975 dollars). This increase, combined with reallocation of funds within the program

to more productive areas, should permit the vigorous pursuit of major program objectives.

The panel believes that a special national targeted program is not desirable at this time.

TOOTH IMPLANTS

Mr. NATCHER. With regard to tooth implants, it is stated in the justifications that we have before the commitee that results of a long-term animal study expected during fiscal year 1977 may lead to clinical trials. Tell us, if you will, when you would initiate such trials. Do you have any idea at this time?

Dr. SCOTT. That would be a very difficult answer to give you at this moment, sir.

As you know, there has been nationally, both on our recommendation and the recommendation of the American Dental Association, a statement of the need to be very careful to get good basic information on implants before they are tried clinically. I think what was happening was that there was a great enthusiasm for implants as a very potent weapon against the inability to retain dentures and bridges or replace missing teeth, and so on. Utilization was beginning to move rather quickly, with limited knowledge and the actual potential of these implants to be retained. Safety was not really a problem as far as generalized immune reactions was concerned. But basically it was retention and loss and that sort of complication. So there was a general agreement to ask the profession to move more slowly.

In the meantime, the research that has been conducted, largely under our support, has been towards getting a better material that has a proven prospect of being retained. This has been going on in primates, baboons mainly, some in other animals. The most promising materials right now seem to include some ceramics. Titanium has come forward again as a material that is handled quite well by the tissue systems. And more recently, I happen to have been involved in some of this myself, at Case Western Reserve University in Cleveland, with a couple of graduate students and faculty in the School of Engineering, with vitreous carbons which have shown promise.

The way things stand now is that the last three types of implants seems to be most promising in the way the tissue holds them, and the way the bone permeates them.

I am not sure quite when this is all going to be completed. Unless my colleagues know the date they think the materials should be ready to put into clinical tests, I would hesitate to guess.

Dr. GARDNER. I would think there is a possibility we might have a very limited study using humans during the next year—not in terms of a clinical trial.

Mr. PATTEN. Congressman Natcher?

Mr. NATCHER. I yield.

Mr. PATTEN. What did George Washington use?

Dr. SCOTT. George Washington used artificial teeth that have been reputed to have been wood. As it turns out—I just heard a paper the other day on this—the only wood in them was little pegs to hold the artificial teeth in. He had, as you know, about as many sets of teeth as he had beds. And the best guess is that they came from walrus, from hippopotamus, cattle, humans, and also some early ceramics.

Mr. PATTEN. They claim that some of his teeth came from hippopotamus material.

Dr. SCOTT. I think the basis for that was there was a large enough body of dentin in the tooth so that a block, a cube, could be cut from it, and second the curvature was such that contours could be obtained. So they looked for big sources of material—ivory tusks were used many years ago, just from sheer size.

DIABETES

Mr. NATCHER. Doctor, in your opening statement you referred to the 1974 Diabetes Act. What role will your Institute play in the development of a coordinated research program in diabetes?

Dr. SCOTT. I think the coordination will come from other quarters, basically. But our contributions to the program, which might be a better way to put it, will fall in two areas. One of them, of course, is the area of virology, in which we are very strong. As you know, there are certain virological implications of diabetes.

The second area relates to the diabetic complications in the oral cavity, which take the form of periodontal disease. We do have work going on in the extramural program along the latter lines, and as I mentioned, along the former lines in the intramural program.

Our current expenditure is about half a million dollars a year. We don't anticipate much change in the 1977 fiscal year, and time will tell where our negotiations about the whole matter will go from there.

TRAVEL

Mr. NATCHER. Doctor; your request for travel averages out to about $1,150 per permanent position. This is an increase over last year's average. But more importantly, it represents a rate per position that is substantially greater than the rate requested by the Arthritis Institute. Why is this so, Doctor?

Dr. SCOTT. I checked that over, listening to the last testimony, and I find that included in that rate is travel for consultants, review people and so on. So I am not sure that you can take that number and divide it by our number of personnel, and come out with a valid number. We will be glad to prepare one for you.

Mr. NATCHER. Suppose you do that.

Dr. SCOTT. It is inseparable at this point from a lot of other items included in it.

[The information follows:]

The actual average cost per permanent position is $899, excluding travel for consultants and review personnel.

Mr. NATCHER. Thank you, Doctor. Mr. Michel.

VIEW OF INSTITUTE

Mr. MICHEL. Thank you, Mr. Chairman.

Doctor, you were once with NIH, and then went out into the world of academia again, and come back to us from being the dean of Case Dental School.

Do you have a different view of the Institute now than you had before you left?

Dr. SCOTT. It is kind of hard to say, sir.

I have noticed changes, but I am not sure they are not for the better. I think that I realized two things outside. One was the high regard in which the place is held, not only nationally, but internationally. And secondly, the tremendous degree of dependency that dental research has on NIDR, in contrast to many other areas of medical research.

If I can just take a second, and trace a little history for you—back in 1948, when I had already been at NIH 4 or 5 years, the new NIDR was a very small operation, but indeed dental research itself was small. At the national meeting there were 100 oral papers given on dental science. The International Association for Dental Research consisted of 600 people. Now, in 1976—I know these facts because I'm the president of the association this year—there are almost 5,000 members in the association, 3,000 of whom are American, and at this year's meetings in Miami, there will be almost 1,100 papers given, 11 times as many.

So dental research is largely in its thrust a post-World War II phenomenon. It started from essentially ground zero. And almost all support, three quarters of it, has come from NIDR. So the impact of NIDR on dentistry and dental research has been far and above what any other Institute can claim.

DENTAL CARE

Mr. MICHEL. Do we have a better level of dental care in this country today than we had 10, 20 years ago, if you take the country as a whole?

Dr. SCOTT. It depends on how you define "level." Do you mean quality care or quantity?

Mr. MICHEL. Well, first let me back up and say, the overall condition of American people so far as their dental needs—are we in better shape today as a country than we were 10, 20 years ago?

Are we making improvements or going backward?

Dr. SCOTT. There is no question we are making improvement. But it would strike me that when we have to face the fact that only 49 percent of the public are getting dental care, there is more improvement needed. So far as the quality goes, there is no question that technological advance has improved the quality.

Mr. MICHEL. Do we have any comparative figures between our country and others with respect to the condition of dental health as a country?

Dr. SCOTT. World Health has some figures, but they are not terribly pertinent to this. I think it would be a difficult comparison to make. I think the general feeling is that this country can hold its own.

EXTRACTIONS

Mr. MICHEL. As a general rule, weren't we doing more extraction years ago than we are today?

Dr. SCOTT. I would say, yes, sir, that extraction has decreased for two reasons. One is technological advance, the ability to preserve teeth; and second, a certain amount of public awareness now that it may be better to have teeth than not to have them.

As I say, the message has not reached far enough yet, by a long shot. But basically those people who do receive care are much more con-

scious of the need to save their teeth, and on the other side of the coin the dentists have better tools with which to save them.

I am not sure there was ever much frivolous tooth extraction, but dentists have been faced with conditions that have no solution except removal of the tooth. Nowadays they have techniques to work with to save the teeth and have been highly trained in this for many years in the schools.

DENTAL SCHOOLS

Mr. MICHEL. How many dental schools do we have today?

Dr. SCOTT. There are 59 now, and one planned in Oklahoma.

Mr. MICHEL. And a mounting list of applicants to dental schools?

Dr. SCOTT. There has been so far, yes.

Mr. MICHEL. What does it take for a young dentist after he graduates from dental school today to go into practice?

Dr. SCOTT. That, sir, is a little difficult to answer because there are so many ways to go in practice. As a dean, of course, I was deep in this, and young graduates today seems to follow fairly common patterns.

There is a little reluctance on the part of many to walk right out of school and go directly into practice. On the one side, there is a fear they might not know enough, so they seek, in large numbers, internships, residencies. A certain number of them seek specialty training, and so they defer entry into practice for a couple of years. Another group seeks research training.

Others, of course, go into the military and a final group, which is relatively smaller than expected goes directly in practice. At one time or another almost all do enter some form of practice.

Now comes the decision of whether to go out individually the way the oldtimers did, and rent a solo office or go into group practice. What you normally find is that the young people at graduation will very often associate for a year or two and make no real expenditure on equipping an office until they are sure of many things, their own desires, their own skills, the type of community they wish to practice in, and the economics. When it is all said and done, I suppose nowadays it would cost something on the order of $30,000 to $50,000 to equip an office for a single individual who had two or three operatories in which he wanted to practice in modern style.

HYGIENISTS

Mr. MICHEL. Did you train dental hygienists at your school?

Dr. SCOTT. No; we did not have a hygiene school.

Mr. MICHEL. But those are on the increase, at least the number being utilized and trained, are they not?

Dr. SCOTT. Yes.

Mr. MICHEL. Are we meeting the need, do you think?

Dr. SCOTT. That, again, is a difficult question to answer, because it is dependent on the desire of the dentists themselves and the economics of the situation. I have some data on this but I think it pertains to numbers, and not needs. I can take a quick look and see. These are data I sought out for my own information. I am familiar with these matters, having been in the academic business, but I wanted to find

out how Health Manpower felt about this. As a result of a conference with them, any figures I give you will be derived from that information as well.

They do not here discuss the need. Certainly the active list of hygienists, as you say, has gone up even in the last 5 years from 15,000 to 28,000. That is quite a jump. How many dentists are using them is a good question. There are 100,000 dentists, so the question is if more hygienists are needed, and I can't answer that. If every dentist or group were to have a hygienist, many more would be needed. But again it is a matter of practitioner preference.

DIRECTION OF DENTAL RESEARCH

Mr. MICHEL. Are we going in the right direction now in your judgment on dental research out at the Institute these days?

You are taking over now. You can look at it from a variety of points of view.

Do you have any dramatic change you would like to institute, or just slight adjustments?

Dr. SCOTT. I think your last words were probably more apropos to my first 6 weeks of observation. There is no question in my mind that all of the pertinent areas in research are covered, that things are not being neglected in the areas of basic knowledge. However, whether the balance is exactly as I personally would like to see it later on, I can't say yet, but that is the kind of thing I would address myself to.

I think that we must do something about the shortage of clinical scientists and clinical research. Budgetwise we are devoting about 25 percent to that and one would hope, of course, that the balance kept swinging so that more got into clinical research and eventually clinical demonstrations.

I also have a feeling that we should be looking harder at behavioral science. This is now a relatively highly developed skill area in research and so much of our success in the ultimate depends on that. It is fine to have preventive methods, but the next question is to develop motivation, find out why these 51 percent of the people are not receiving dental care.

Mr. MICHEL. Do we have figures to show that? Is it cost?

Dr. SCOTT. I think some of it must be cost-related, of course, but I think there is a lot more to it than that. There is a whole matter of attitudes toward dentition as well as dentists, the values placed on dental care.

Mr. MICHEL. As long as I don't get a toothache, why go?

Dr. SCOTT. Absolutely. I think, though, that behavioral research should be emphasized. We should look for ways to support it. We are doing some of it ,but I think that might be an area where the balance should be a little more in that direction.

I think, looking over the whole Public Health Service, that we do need to activate studies in various aspects of fluoride research, which are aimed at expanding our knowledge, and I can see this as an area where we should be more active.

ORTHODONTISTS

Mr. MICHEL. Do you have more students becoming orthodontists, as distinguished from a few years back? That seems to me to be a real shortage area again. You wait and wait for months for an appointment sometimes.

Dr. SCOTT. That is one of the more popular specialties. Dentistry is a rather different profession, as you know. It is the reverse of medicine, which is 85 percent specialists. Dentistry is about 12 percent specialized. The highest numbers are in oral surgery and orthodontics. There are many applicants for the programs in orthodontics. I would say also that, in the educational arena, there is a trend now to train nonspecialized dentists in relatively simple, so-called minor tasks in orthodontics and movement of teeth so that the skills of the orthodontist can be left to the more difficult cases. That is, in a way, a real advance, and I think it is a very healthy development.

DENTAL CARE

Mr. MICHEL. Well, in the infantry days you didn't get to brush your teeth and I think I had to go to the dentist once or twice before entering the service and, when I was out, I had to have 3 pulled and 14 filled and that was a lesson for me.

Ever since that time I have always gone twice a year. Those dental hygienists have cleaned my teeth twice a year and my dentist takes a look-see where we are; they do a terrific job and there is no need to tie up the high-priced time of the doctor doing those routine kind of things. But, for me, I feel it is very satisfactory and for the kids, too.

PREVENTIVE MEDICINE

Mr. MICHEL. The Dental Research Institute, possibly more than any other institute, can and should be taking a very active role in the areas of preventive medicine. Would you outline for us your programs directed toward educating practitioners and the public in the latest findings regarding dental hygiene? How successful have these programs been?

Dr. SCOTT. I am happy to report that we are stepping up our efforts to reach the practitioners and the public with the latest research findings related to prevention of dental and oral diseases.

One important approach to the practitioner is the regular participation of the National Institute of Dental Research staff in meetings of the various national dental organizations, as well as of local dental societies, dental alumni groups, and other professional organizations. Since 1976 represents the 5-year point for the institute's national caries program, plans have been developed to present extensive reports on current research findings and leads for the future at the annual meetings of both the American Dental Association and the National Dental Association. Also, for the first time, a detailed progress report was presented in February before combined faculty and student bodies of the University of Pennsylvania and Temple University. In succeeding

years, similar reports will be made to other national organizations as well as at regional meetings of dental societies.

The outreach to the practitioner is further extended by the publication of proceedings of selected meetings as well as individual reports in the professional press.

Another productive avenue of communications is the monthly mailing of releases on selected research findings to dental schools, research institutes, and periodicals read by dental practitioners.

More recently, still another service has been initiated. This is a series of state-of-the-art film reports intended for dental students as well as for showing at meetings of dental societies. The first one, on the prospects for a caries vaccine, was produced in 1974 and premiered in the fall of that year at the annual meeting of the American Dental Association. Subsequently, multiple prints were made available to the National Medical Audiovisual Center at Atlanta, Ga., for promotion and free loan to dental groups. The second film is on the use of topical fluorides to prevent caries. It, too, was shown at the American Dental Association's national meeting, and prints will soon be available for free loan. A third film, dealing with sealants in caries control, is now being developed.

Finally, the programs launched by the National Institute of Dental Research in late 1975 to demonstrate the cost-benefits of fluoride mouthrinsing programs in schools have an educational component, both for the profession and the general public.

We plan to develop a news film feature on these programs to be made available to television stations in the spring of 1976. Next year, we plan to prepare television spot announcements for more widespread distribution to elicit greater interest in adoption of this preventive technique.

Information for the public is regularly provided by the institute to the media through "Research Capsules from the National Institute of Dental Research," mailed to interested science writers, responses to direct inquiries from popular periodicals, and contributions to the National Institutes of Health communications channels. One such channel is a National Institutes of Health News and Feature Service, distributed monthly to about 600 domestic professional journals, medical and dental news publications and magazines, and to major newspapers in this country. The second is the National Institutes of Health Search for Health series of weekly newspaper columns distributed to about 500 weekly and several small daily newspapers in the United States.

Dental research is well represented in these mailings as well as in the radio spot announcements distributed by the National Institutes of Health to more than 2,000 radio stations throughout the country subscribing to this service.

In addition, the National Institute of Dental Research has prepared publications dealing with dental decay, plaque, periodontal disease, nutrition and dental health, and oral ulcerations, which it makes available to the public on request.

It is impossible to determine the full impact of these informational efforts. One measure, however, is the use of the various communicating services. It is known, for example, that the monthly releases provided by the National Institute of Dental Research to professional

journals are used extensively. Similarly, inquiries from the lay press are triggered by materials developed by the institute. A greater flurry of requests for pamphlets is also evident following the use of radio spot announcements on dental subjects. Finally, a great amount of interest is expressed by teachers at annual meetings of the National Science Teachers Association and the National Association of Biology Teachers, where the National Institute of Dental Research exhibits are regularly shown.

FLUORIDE MOUTH RINSING

Mr. MICHEL. You make reference in your statement to the program of weekly fluoride mouth rinsing in school classrooms. Is this thought necessary only in those communities without fluoridated water?

Dr. SCOTT. Thus far our demonstration programs of fluoride mouth rinsing are located only in communities which do not have fluoridated water. We are conducting studies now to find whether mouth rinsing will provide added protection in fluoridated communities, but these studies are not yet complete.

Mr. MICHEL. The approximate reduction of 40 percent in tooth decay under such a program—is that a pretty solid figure?

Dr. SCOTT. It is never possible to predict the exact level of protection. Fluoride mouth rinsing has been tested in over 20 controlled clinical trials. Most of these studies have shown protection against caries in the range of 20–50 percent. We believe that a protection of around 40 percent is a reasonable expectation in these programs.

Mr. MICHEL. About what would it cost per child per year for the operation of such a program?

Dr. SCOTT. The fluoride mouth rinse, paper cups, and similar supplies can be obtained commercially for about $0.45 per child per year. Since supervision of the procedure is well within the capabilities of the classroom teacher, and requires only 5–10 minutes per week, personnel costs should also be extremely low.

AREAS OF RESEARCH

Mr. MICHEL. Some of your research endeavors, such as that pertaining to viral infections and craniofacial anomalies appear to range rather far afield. At least you make reference in your statement to the impact a number of your research efforts have in other areas of human health. Are you getting away from strictly dental research?

Dr. SCOTT. The National Institute of Dental Research is primarily concerned with dental diseases and other abnormal conditions. An understanding of these problems is dependent upon a broad underpinning of fundamental science. Thus, when we study the basic virologic or immunologic phenomena involved in herpetic disease (oral fever blisters) or the underlying causes of craniofacial anomalies, such as cleft palate, it is a natural consequence that the results may also find application in an understanding of other conditions. It might also be noted that there are often significant similarities between certain diseases. For example, the inflammatory process associated with periodontal disease is very similar to that associated with arthritis. It is not at all unusual that findings in one system may apply to the other.

Mr. MICHEL. Have you established any basic perimeters which are designed to focus research in a dental direction?

Dr. SCOTT. The National Institute of Dental Research has developed and is following a long-range plan which does focus research in dental problems. Reorganizations of the intramural programs in recent years have served to bring a direct focus on dental problems and to extend the findings of the basic science laboratories into clinical investigations. The dental orientation also holds true for extramurally supported research. Whereas initial review groups are concerned with scientific merit, the National Institute of Dental Research staff and the National Advisory Dental Research Council direct primary attention to program relevance of grant applications.

BUDGET DATA

Mr. MICHEL. According to your justifications, there appears to be a doubling of something called the HEW general expense assessment—an increase of $654,000 over the 1976 level of $680,000. What is that?

Dr. SCOTT. The DHEW general expense account includes the following: upward mobility-department and National Institutes of Health programs; departmental overhead-working capital funds and departmental management projects and National Institutes of Health overhead-career development programs and administrative support services. Program evaluation is also included, and it represents the systematic assessment of existing programs to determine the extent to which they achieve their established objectives. The fiscal year 1977 projection represents annualization of the prior year assessment plus an increase based on the percentage higher the fiscal year 1976 estimate was than the fiscal year 1975 actual obligations.

Mr. MICHEL. There is also nearly a doubling of rents, communications, and utilities, from $265,000 to $467,000. How do you account for that large of an increase?

Dr. SCOTT. This increase represents additional costs for standard level user charge related to rental of space, and for postage, and Federal telecommunications system. All of these are built-in or mandatory items, the first accounting for most of the increase.

Mr. NATCHER. Mr. Patten?

ORAL CANCER

Mr. PATTEN. You never mentioned the word cancer as far as I can recall in your presentation. This $800 million we have in the Cancer Institute, are you fellows in on that in any way?

Dr. SCOTT. Basically, I think the answer to that is that the responsibility there does fall with the Cancer Institute by agreement. It is their extramural program that will be supporting oral cancer research.

Dr. GARDNER. We collaborate with them and work with them on developing studies on oral cancer.

Mr. PATTEN. One friend of mine couldn't understand how his oral cancer progressed so far since he had been to the dentist regularly. The insinuation was that the dentist didn't see it early.

Dr. SCOTT. I might make one remark. For the last, I suppose 10 or 12 years, there have been very intensive programs in the dental

schools in cancer detection that were supported by the National Cancer Institute. These programs have been very effective in training dental students and in the continuing education of practicing dentists. These are programs that are run for several days annually. In Cleveland several hundred dentists were attending.

Essentially everybody has taken this program at one time or another, in which they learn how to make a good oral cancer examination, lymph node examination and even a biopsy. So the training in that is pretty heavy these days.

DENTAL CARE FOR AGED

Mr. PATTEN. A lot of our senior citizens living on social security or otherwise oppressed for one reason or another, don't go to the dentist. This is not your job but I am just wondering if there is special bit to be done for senior citizens. Aren't there special problems for the older citizens that we could well spend time on? Nothing was said here particularly in reference to age.

Dr. SCOTT. I suspect, Mr. Patten, that there are special problems in aged people as far as retention of dentures and flattening of bone and the like, but these are basically technical problems. There are also, of course, some psychological problems. I doubt if there are serious nutritional problems, because in our culture one can survive nutritionally without teeth or dentures. Basically, I think the psychological and emotional problems, as well as certain constructional problems for dentures can be acute. Inaccessibility of service would also be a major hurdle.

Mr. PATTEN. You mentioned you are fooling around with other materials that may have more strength for use in dentures.

Dr. SCOTT. Yes; that is quite correct.

Mr. PATTEN. Do you think you have something?

Dr. SCOTT. I am not sure where that stands right now.

Dr. GARDNER. Mr. Chairman, if I might elaborate just a little bit on this, one of our major concerns in addition to looking at different materials for dentures and other prosthesis is to hopefully reduce the cost.

I think, Mr. Patten, that this is one of the real hardships for many of the older people, to pay the tremendous cost for a set of dentures or even a partial.

Dr. SCOTT. Actually, it is rather interesting that one of the major benefits, though, of the welfare system in cities, for example, or States, and of various other public programs has been dentures for the aged. That has been one of the major benefits of these programs.

Mr. PATTEN. I know the senior citizens are in a bind. They don't have it.

NATIONAL CARIES PROGRAM

Mr. NATCHER. Mr. Conte.

Mr. CONTE. Can you describe the national caries program?

Dr. SCOTT. Yes, sir. The national caries program is a highly targeted research and development program with the mission of developing methods to prevent dental caries to the point where this disease will no longer be a major public health problem. The program began in 1971 as a special Presidential initiative. The national caries program

conducts and supports a wide variety of laboratory and clinical research, and community demonstrations, with four major research strategies: combating the microbial agent, increasing tooth resistance, altering the harmful properties of the diet, and improving delivery and public acceptance of preventive methods. The program uses grants, contracts, and direct research to accomplish its mission. We feel that we have made substantial progress toward eventual prevention of dental caries, but the problem is far from being solved.

SEALANTS

Mr. CONTE. How well are the recently developed tooth sealants working?

Dr. SCOTT. As I mentioned in my opening statement, the type of sealant which we have been researching for the past 5 or 6 years—an ultraviolet light—polymerized plastic—has now been proved safe and effective in a series of field trials. The sealant has been retained for over 2 years on as many as 60 percent of the treated teeth. Caries has not occurred on the surfaces of the teeth where the sealant remained in place.

BUDGET DATA

Mr. CONTE. What type of positions are the 13 you indicate will be dropped?

Dr. SCOTT. The decrease in positions would consist of six professional and seven support personnel.

Mr. CONTE. Would you explain why on the table on page 104 indicates a decrease of seven positions yet an increase of $1,054,000?

Dr. SCOTT. This increase is due to built-in mandatory items, such as general expense, program evaluation, postage, Federal telecommunications system, annualization of the pay raise, cost of within-grade salary increases, travel, and National Institutes of Health management fund.

HOME DENTAL CARE

Mr. CONTE. What advances in home dental care have you made in the past year?

Dr. SCOTT. Home dental care involves the use of fluoride dentrifices, topical fluorides if prescribed by a dentist, reduction of sugar-containing snack foods and thorough removal of plaque from the teeth by brushing and using of dental floss. During the past year we have continued our research on improved topical fluorides and dietary sugar substitutes. One of the latter, called xylitol, appears promising, and will shortly be tested in a controlled clinical trial. In addition, we have continued two studies of the ability of children to effectively brush and floss their teeth and, in another study, we are investigating the attitudes and motivation of children toward personal oral health care.

PUBLIC EDUCATION RESEARCH

Mr. CONTE. Have you looked seriously at public educational research in the dental field? I mean, getting advances in home care techniques to those who should use them?

Dr. SCOTT. We are aware that merely informing the public of preventive advances is not sufficient. It is an important first step but

needs to be reinformed by behavioral studies to determine how people can be motivated to use the information. Our concern with this problem is illustrated by the fact that one of the major strategies of the national caries program includes study of acceptance of preventive techniques by the public, once the techniques become available.

A beginning has been made in this area with a study now under way to determine attitudes and motivation of children toward dental health and hygiene. In addition, we have just added to the staff of the national caries program a health education specialist, who will be responsible for developing further research on this subject.

UNFUNDED RESEARCH GRANTS

Mr. CONTE. How many approved, but unfunded research grants will you have this year?

Dr. SCOTT. There will be approximately 165 unfunded.

MAJOR DENTAL PROBLEMS

Mr. CONTE. What do you feel is the major dental problem facing the American public?

Dr. SCOTT. Mr. Conte, there is no question that the major dental health problem in this country is twofold; namely, dental caries and periodontal disease. Caries affects nearly 100 percent of the population. Its progressive incidence is greatest in children and adolescents, but it is obviously a disease that continues in adulthood. After age 25 or 30, periodontal disease becomes a major problem and this causes most of the tooth loss in older people. Finding ways to prevent these major chronic diseases continues to be a primary research goal.

BUDGET

Mr. CONTE. Do you feel that the budget you are proposing adequately addresses this problem?

Dr. SCOTT. The budget for the national caries program is essentially unchanged from the preceding year. Considering the position and fiscal levels, we will experience difficulties in our intramural laboratory studies, in our drug screening efforts, and in the important areas of demonstration, information, and investigative behavioral science. The same picture holds for our programs in periodontal research, where we will encounter difficulty in moving ahead in the areas recommended by our external evaluation committee. These recommendations have been included earlier in my testimony, and I believe they are right to the point—clinical research within the National Institute of Dental Research and extramurally, cooperative ventures and training of clinical investigators.

NUTRITION

Mr. ROYBAL. You indicate that nutrition is an important factor in caries, enamel defects, disturbances of salivary gland function, and increased permeability of the mucous membrane to bacterial endotoxin. What nutrients have you identified as important to good care?

Dr. SCOTT. Longstanding evidence has shown the need for adequate general nutrition. More recent studies have shed new light on the special needs for sufficient protein, vitamins C, A, and D, and trace ele-

ments. These dietary components play roles in the conditions you mention, and we are beginning to understand the mechanisms involved. Sugar—sucrose—of course, is well known as a causative factor in dental caries. Fluoride continues to be the chief preventive against tooth decay.

Mr. ROYBAL. What foods supply these nutrients?

Dr. SCOTT. In the case of proteins, the best sources are meat, fish, poultry, milk, cheese, eggs, cereals, nuts, and some vegetables, such as beans and peas.

Vitamin C is found in fresh fruits—citrus—and fresh vegetables. This vitamin cannot be stored in the body and thus must be supplied daily. Vitamin A can be obtained from egg yolk, butter, cheese, milk, and vegetables. Vitamin D is produced to some extent from sunshine on the skin but is also found in fortified milk.

Fluoride supplementation, in nonfluoridated areas, is achieved through water fluoridation or addition of fluoride to the diet.

Mr. ROYBAL. Does the diet of a low-income person and his family tend to lack these nutrients?

Dr. SCOTT. It is safe to assume that low income could result in the inability of people to purchase adequate quantities of meat, milk, eggs, fresh fruits and vegetables, et cetera. In some cases, however, lack of knowledge or poor food selection habits may be responsible for inadequate nutrition even in people with adequate income.

Mr. ROYBAL. The Federal Government sponsors a number of programs that supply food to low-income children, such as the school lunch program, and Headstart. Do you feel that these programs are important in supplying the nutrients that are deficient in the diets of low-income children?

Dr. SCOTT. Food programs for low-income children are certainly very important, and they can indeed provide necessary nutrients. We would, however, discourage inclusion of snack foods or baked goods which are high in sugar content and of dubious nutritional value, because of their known contribution to dental caries.

FLUORIDATION

Mr. ROYBAL. I have received quite a bit of mail expressing concern about the health hazards posed by fluoridation. Is there any health hazard associated with fluoridation that you have identified?

Dr. SCOTT. No, sir, there is not. This question has been extensively examined for years by scientists in many countries. Fluoridation is a safe and effective public health measure and is fully endorsed by major scientific and health organizations. Just recently the British Medical Council concluded 2 years of study on fluoridation and has added its endorsement of safety and effectiveness to a very long list of prestigious organizations throughout the world.

Mr. ROYBAL. How many communities utilize fluoridation treatment in their water?

Dr. SCOTT. The best current estimate is that 6,000 communities have adjusted the fluoride content of their water for maximum protection against tooth decay. Another 2,600 communities have natural fluoride at optimum or higher levels. All told, about 100 million Americans have the benefit of either natural or adjusted fluoridation. This is

about 46 percent of the population and about 60 percent of those using public water supplies.

Mr. ROYBAL. What statistics can you cite which indicate the effectiveness of fluorides as a protector of teeth?

Dr. SCOTT. The statistics from dozens of controlled studies of fluoridation in the United States and in other countries have been remarkably consistent in showing a 50-percent to 60-percent protection against caries in persons who drink fluoridated water from birth. Many studies have also demonstrated substantial levels of protection from fluorides applied topically to the teeth after they erupt.

FIGHT AGAINST CARIES

Mr. ROYBAL. You indicate that you have developed some compounds that are now being used in the fight against caries. Who markets these compounds?

Dr. SCOTT. Most of the new compounds now being tested as potential caries-preventive agents have been synthesized by pharmaceutical companies. The National Institute of Dental Research does not have the capabilities to undertake this process. None of these compounds is yet being marketed.

Mr. ROYBAL. If the large pharmaceutical companies do the marketing, why should they profit from the Government's research?

Dr. SCOTT. We believe that it is in the public interest to stimulate the development and eventual availability of chemotherapeutic agents which will help prevent dental caries. Most of these compounds have no other medical use and probably would not otherwise be developed by the pharmaceutical manufacturers. Much of the rigorous scientific laboratory screening, animal, and clinical trials thus falls to the National Institute of Dental Research. Even though we conduct, or select contractors to conduct this necessary animal and clinical research, the manufacturer must still make a substantial investment to produce the toxicity and quality control data required by the Food and Drug Administration before human trials and marketing are permitted.

Mr. ROYBAL. Do they pay a royalty?

Dr. SCOTT. Our program to screen these compounds involves an agreement with each participating manufacturer. These agreements are developed with the advice and approval of the National Institutes of Health patent attorneys. They include the provision that the Government has a royalty-free, nonexclusive license to produce and use the compound for caries prevention. Of course, if a compound is first discovered by a commercial firm during research supported by a Government contract, this compound may be patented by the Government. Frequently, however, the Government would assign the rights to a commercial firm as an incentive to invest risk capital to develop the compound for marketing.

Mr. ROYBAL. If not, what reimbursement arrangement is used?

Dr. SCOTT. Reimbursement arrangements are not used.

Mr. NATCHER. Dr. Scott, we want to thank you and your associates for appearing before the committee at this time. As I said before you started, we have had two good presentations. This is the third one, and we will now stand adjourned until 10 o'clock in the morning. Thank you very much.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Amounts Available for Obligation

	1976 Estimate	1977 Estimate
Appropriation	$45,794,000	$52,207,000
Request Pending	5,497,000	---
Subtotal adjusted appropriation	51,291,000	
Comparative transfer from:		
"Office of the Director, NIH" (Transfer of the Standard Level User Charge)	+136,000	---
Total, obligations	51,427,000	52,207,000

National Institute of Dental Research
Mechanism Table

Grants	FY 1976 No.	FTE	Amount	FY 1977 No.	FTE	Amount
Regular						
Noncompeting	260		14,600,000	322		17,282,000
Competing	81		4,304,000	55		2,694,000
Subtotal	341		18,904,000	377		19,976,000
Special						
Specialized Research Centers	1		342,000	1		342,000
Dental Research Institutes	6		7,200,000	6		7,200,000
Research Career Program	25		582,000	25		615,000
Scientific Evaluation	1		65,000	1		76,000
Subtotal	33		8,189,000	33		8,233,000
Total Grants	374		27,093,000	410		28,209,000
Fellowships						
Noncompeting	75	189	3,044,000	24	94	1,565,000
Competing	0	0	0	0	0	0
New	0	0	0	17	17	300,000
Supplemental	0	0	0	0	0	0
Subtotal	75	189	3,044,000	41	111	1,865,000
Training Grants						
Noncompeting	34	123	2,297,000	16	65	1,266,000
Competing	0	0	0	0	0	0
New	0	0	0	0	0	0
Supplemental	0	0	0	0	0	0
Subtotal	34	123	2,297,000	16	65	1,266,000
Intramural Research and Direct Operations			11,967,000			13,047,000
Research and Development Contracts	63		4,908,000	70		5,408,000
Program Management			1,982,000			2,101,000
Standard Level User Charge			136,000			311,000
Total	546		51,427,000	537		52,207,000

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN OF 1977 JUSTIFICATION

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	Intramural Research and Direct Operations	Research and Development Contracts	Program Management	Total
1. Caries.....	3,242	1,161		146	94	297	1,569	3,208		9,717
2. Periodontal Diseases.....	3,621	737		72	485	997		560		6,472
3. Restorative Materials.....	1,550	566		46	469	29		400		3,060
4. Craniofacial Anomalies.....	3,995	971	342	112	602	1,075		300		7,397
5. Pain Control and Behavioral Studies	687	393		65	487	108		100		1,840
6. Soft Tissue, Stomatology and Nutrition.....	1,505	476		206	160	538		340		3,225
7. Dental Research Institutes.....			7,200							7,200
8. Intramural Research & Direct Operations							10,534			10,534
9. Program Management..									1,982	1,982
Total obligations.....	14,600	4,304	7,542	647	2,297	3,044	12,103	4,908	1,982	51,427

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DHEW - National Institutes of Health

CROSSWALK - 1977 COLUMN OF 1977 JUSTIFICATION

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	Intramural Research and Direct Operations	Research and Development Contracts	Program Management	Total
1. Caries	3,855	607		187	79	221	1,617	3,313		9,879
2. Periodontal Diseases	4,320	532		75	265	627		616		6,435
3. Restorative Materials	1,901	332		47	325	20		400		3,025
4. Craniofacial Anomalies	4,666	621	342	114	311	418		600		7,072
5. Pain Control and Behavioral Studies	812	352		67	126	97		100		1,554
6. Soft Tissue, Stomatology and Nutrition	1,728	250		201	160	482		379		3,200
7. Dental Research Institutes			7,200							7,200
8. Intramural Research & Direct Operations							11,741			11,741
9. Program Management									2,101	2,101
Total obligations	17,282	2,694	7,542	691	1,266	1,865	13,358	5,408	2,101	52,207

Summary and Explanation of Changes

1976 Estimated obligations	$51,427,000
1977 Estimated obligations	52,207,000
Net change	+780,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Within grade increases		$4,149,000		+$85,000
2. Postage increase		77,000		+4,000
3. FTS increase		14,000		+3,000
4. Travel increase		266,000		+40,000
5. Bureau of Employee Compensation increase		10,000		+1,000
6. Service and Supply fund increase		624,000		+120,000
7. Program Evaluation and DHEW General Expense Assessment		680,000		+654,000
8. Annualization of 1976 pay		354,000		+109,000
9. Payment to the NIH Management Fund		2,493,000		+205,000
10. Standard Level User Charge		136,000		+175,000
Subtotal				+1,396,000
B. Program:				
1. Research grants:				
a. Noncompeting grants-continuing support of 108 grants from 1976 and Transitional Quarter		14,600,000		+7,108,000
b. Support of 55 Competing grants		4,304,000		+2,694,000
c. Special grants-increase in stipend for 1976 awards and Scientific evaluation grant		647,000		+44,000
d. Contract increase for support of 7 new Research & Development contracts		4,908,000		+500,000
e. Support of 17 new fellowships		0		+300,000
Subtotal				+10,646,000
Total, increases				+12,042,000

Decreases:				
A. Built-in:				
1. One day less pay.....		22,000		-22,000
2. Decrease in positions...	282	0	-13	0
Subtotal.....		---	-13	-22,000
B. Program:				
1. Research grants:				
a. 46 Noncompeting grants completed, converted, or terminated.....		14,600,000		-4,426,000
b. 81 Competing grants converting to non-competing status.....		4,304,000		-4,304,000
2. Fellowships - phase-out from old Fellowship program of 34 grants.....		3,044,000		-1,479,000
3. Training - phase-out from old Training program of 16 grants.....		2,297,000		-1,031,000
Subtotal.....		---		-11,240,000
Total, decreases.....		---	-13	-11,262,000
Total, net change.....		---	-13	+780,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
		Amount	Amount	Amount	Amount
113	Caries	$9,055,000	$9,700,000	$9,840,000	+$140,000
	Positions	34	39	34	-5
115	Periodontal Diseases	5,935,000	6,472,000	6,435,000	-37,000
117	Restorative Materials	2,651,000	3,060,000	3,025,000	-35,000
119	Craniofacial Anomalies	6,746,000	7,397,000	7,072,000	-325,000
121	Pain Control and Behavioral Studies	1,659,000	1,840,000	1,554,000	-286,000
123	Soft Tissue Stomatology and Nutrition	2,949,000	3,225,000	3,200,000	-25,000
125	Dental Research Institutes	7,200,000	7,200,000	7,200,000	---
127	Intramural Research and Direct Operations	10,415,000	10,415,000	11,469,000	+1,054,000
	Positions	205	212	205	-7
129	Program Management	1,982,000	1,982,000	2,101,000	+119,000
	Positions	30	31	30	-1
	Standard Level User Charge	136,000	136,000	311,000	+175,000
	Total obligations	48,728,000	51,427,000	52,207,000	+780,000
	Positions	269	282	269	-13

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	282	269	-13
Full-time equivalent of all other positions	41	41	0
Average number of all employees	326	313	13
Personnel compensation:			
Permanent positions	$5,691,000	$5,825,000	+$134,000
Positions other than permanent	807,000	824,000	+17,000
Other personnel compensation	213,000	220,000	+7,000
Subtotal, personnel compensation	6,711,000	6,869,000	+158,000
Personnel benefits	1,026,000	1,105,000	+79,000
Travel and transportation of persons	266,000	306,000	+40,000
Transportation of things	40,000	40,000	0
Rent, communications & utilities	265,000	467,000	+202,000
Printing and reproduction	75,000	75,000	0
Other services	1,308,000	2,053,000	+745,000
Project contracts	4,908,000	5,408,000	+500,000
Payment to the NIH Management Fund	2,629,000	3,009,000	+380,000
Supplies and materials	1,148,000	1,148,000	0
Equipment	617,000	617,000	0
Grants, subsidies & contributions	32,434,000	31,110,000	-1,324,000
Total obligations by object	51,427,000	52,207,000	+780,000

Significant Items in House and Senate
Appropriation Committee Report

Item	Action Taken or to be Taken
1976 Senate Report	
1. The Committee feels that the Dental Research Institute--possibly more than any other Institute--can and should be taking a very active role in the area of preventive medicine. Further, the NIDR is directed to move ahead rapidly in this area of research dissemination by providing communities, schools, and dental students with the most recent techniques and methods of preventive dental care. The Committee will be anxious to review what has been accomplished in this area prior to the fiscal 1977 hearings. (Page 42.)	1. A report was submitted showing increased efforts by NIDR in recent years, particularly with regard to dental students and practitioners, and the substantially greater effort now under way. It reflects counsel sought from individual practitioners as well as various dental organizations which are concerned with information for the public as well as professional education.

Authorizing Legislation

Legislation	1977 Authorization	1977 Appropriation Requested
Public Health Service Act		
Section 301--Research and Investigation, in general	Indefinite	$49,076,000
Title IV, Part C--National Institute of Dental Research	Indefinite	
Title IV, Part I--National Research Service Award	1/	3,131,000 2/

1/ Authorization expires June 30, 1975, extension legislation is pending.

2/ Funding estimate only.

National Institute of Dental Research

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	45,794,000 4/	45,794,000 4/	
Items Not Considered		(5,497,000)	(5,497,000)	
1977	52,207,000			

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 as authorized by Public Law PL 93-192.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

4/ Excludes training not considered by House and Senate due to lacking authorization.

The figures presented in this Table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of General Research Support Grants is no longer the function of this Institute. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes.

National Institute of Dental Research

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	45,794,000 4/	45,794,000 4/	
Items Not Considered		(5,497,000)	(5,497,000)	
1977	52,207,000			

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 as authorized by Public Law PL 93-192.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

4/ Excludes training not considered by House and Senate due to lacking authorization.

Justification

National Institute of Dental Research

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Caries	$9,055,000	$9,700,000	$9,840,000	+$140,000
Positions	34	39	34	-5
Periodontal Diseases	5,935,000	6,472,000	6,435,000	-37,000
Restorative Matierals	2,651,000	3,060,000	3,025,000	-35,000
Craniofacial Anomalies	6,746,000	7,397,000	7,072,000	-325,000
Pain Control and Behavioral Studies	1,659,000	1,840,000	1,554,000	-286,000
Soft Tissue Stomatology and Nutrition	2,949,000	3,225,000	3,200,000	-25,000
Dental Research Institutes	7,200,000	7,200,000	7,200,000	---
Intramural Research and Direct Operations	10,415,000	10,415,000	11,469,000	+1,054,000
Positions	205	212	205	-7
Program Management	1,982,000	1,982,000	2,101,000	+119,000
Positions	30	31	30	-1
Standard Level User Charge	136,000	136,000	311,000	+175,000
Total obligations	48,728,000	51,427,000	52,207,000	+780,000
Positions	269	282	269	-13

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 1975, NIDR began a formal evaluation of its periodontal disease research activity, including both extramural and intramural endeavors. Inasmuch as this was the first comprehensive evaluation of an NIDR research program, it has been 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 evaluation has been completed. The panel report is being proposed and will be submitted to the Institute Director in January, 1976.

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.

Caries

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Caries	$9,072,000	$9,717,000	$9,879,000	+$162,000
Positions	34	39	34	-5
Budget Mechanism:				
Research Grants				
Regular				
Noncompeting	$3,242,000	$3,242,000	$3,855,000	+$613,000
Competing	516,000	1,161,000	607,000	-554,000
Special	146,000	146,000	187,000	+41,000
Training Programs				
Training Grants	94,000	94,000	79,000	-15,000
Fellowships	297,000	297,000	221,000	-76,000
Research and Development				
Contracts	3,208,000	3,208,000	3,313,000	+105,000
Intramural Research and				
Direct Operations	1,569,000	1,569,000	1,617,000	+48,000
Total	9,072,000	9,717,000	9,879,000	+162,000
Positions	34	39	34	-5

Objectives, 1977:

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 technics 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 technics. The final stage of research and development for each technic involves several years of field testing and cost-benefit evaluation.

Continued emphasis will be given to identification of effective, safe antimicrobials for topical use, development of slow-release delivery vehicles, development of an anticaries vaccine, and testing of sucrose substitutes. Specific objectives include:

1. Begin human trials of 3 antimicrobial agents which have successfully passed intensive in vitro and animal caries screening.
2. Initiate the first U.S. trial of Xylitol as a noncariogenic dietary sucrose substitute.
3. Develop demonstration programs combining fluoride mouthrinsing with adhesive sealants.
4. Expand experimental (primate) vaccine studies to include non-streptococcally-derived antigens.
5. Expand epidemiologic studies on the prevalence and distribution of root-surface caries in adults.

Accomplishments, 1976:

Significant advances were made in several areas of the National Caries Program's research and development efforts. Our extensive field trials of an adhesive sealant to protect occlusal surfaces of teeth were completed, with safety and efficacy of the technic demonstrated. Community demonstrations of the technic are being planned.

Four years of research in our laboratories (in collaboration with the Center for Disease Control) resulted in the development of highly specific antisera to permit identification of 5 serotypes of Streptococcus mutans from human plaque samples. The effect of antimicrobial agents against plaque bacteria can now be closely monitored.

Excellent progress was made toward the development of a slow release system for prolonged, metered delivery of fluoride and other caries-preventive agents in the oral cavity. The NCP primate laboratory became fully operational with over 80 M. fasicularis monkeys undergoing experimental immunization against caries.

Perhaps the most significant accomplishment was the initiation of a Community Caries Prevention Demonstration Program. Nearly 75,000 elementary school children in 17 selected communities began weekly mouthrinsing with sodium fluoride, a highly cost effective preventive method. This marks the first organized, deliberate attempt to translate caries research results into widespread public application.

Periodontal Diseases

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Periodontal Diseases....	$5,935,000	$6,472,000	$6,435,000	-$37,000
Budget Mechanism:				
Research Grants				
Regular				
Noncompeting.....	$3,621,000	$3,621,000	$4,320,000	+$699,000
Competing.....	200,000	737,000	532,000	-205,000
Special.....	72,000	72,000	75,000	+3,000
Training Programs				
Training Grants.....	485,000	485,000	265,000	-220,000
Fellowships.....	997,000	997,000	627,000	-370,000
Research and Development				
Contracts.....	560,000	560,000	616,000	+56,000
Total.....	5,935,000	6,472,000	6,435,000	-37,000

Objectives, 1977:

The Periodontal Diseases Program Branch fosters research related to the cause, nature, diagnosis, treatment and prevention of periodontal disease. The goal of the Periodontal Diseases Program is to eradicate periodontal disease, a major health problem which affects the majority of adults throughout the world. In nearly two-thirds of our middle-aged population, periodontal disease has already destroyed much of the supporting bony tissues and will proceed to tooth loss if not checked.

The disease process begins when sufficient bacterial plaque, a film of organisms, their waste products and food residues, has accumulated around the necks of teeth to produce inflammation in the adjacent gingival (gum) tissues. If gingival inflammation continues unabated, the body's immune responses to the plaque bacteria and also responses of local cells cause a breakdown of connective tissues and bone which hold the teeth firm. Because the disease is insidious and hard to detect at an early stage, it often progresses without warning to an advanced state.

Therefore, the Program will continue to support research on the critical steps in the disease process in order to develop methods to control or prevent it. These studies will encompass the total disease process from the time that the bacteria first begin to grow on tooth surfaces to the ultimate destruction of all periodontal tissues. Studies to learn more about the nature of the bacteria recently isolated from patients with severe periodontal disease will be pursued; and combined laboratory animal and clinical studies will be done to determine whether these organisms actually cause this disease in humans and how they cause it. Animal models which mimic human periodontal diseases will aid in achieving these objectives. When the causal bacteria and their disease-producing mechanisms are definitely known, protective immunization for periodontal diseases may become feasible. Meanwhile clinical studies will test the ability of new chemical agents to prevent the attachment and growth of bacteria on tooth surfaces. Cooperative clinical studies involving several teams of researchers may be initiated in order to pool research talent and patient resources necessary to carry out the research described above.

Accomplishments, 1976:

Seven of the anaerobic bacteria isolated from sites of severe human periodontal disease were studied more closely. Some of these organisms have now been identified as individual species and one group has been placed in a new genus. All of these organisms caused periodontal disease with severe bone loss in otherwise germ-free rats.

Another study showed that a particular periodontal bacterium possessed disease-producing characteristics only when infected with a plasmid. Plasmids are pieces of genetic material (DNA), not packaged in chromosomes which can infect bacterial cells and give them harmful qualities. It is generally accepted that bacterial endotoxins (poisons) from the periodontal plaque seep into the gingival tissues and trigger inflammation and destruction of tissues. During the past year, however, investigators have found another role for this substance. Endotoxin also becomes absorbed to tooth roots exposed by periodontal disease. When human tooth roots with absorbed endotoxin were placed in tissue cultures with gum tissue cells, the cells did not attach to the root surfaces. However, subsequently when the endotoxin was removed from the roots, gum cells did attach. Since the absorbed endotoxin prevented cells from attaching in the laboratory, it is likely that this substance may also prevent reattachment in a similar manner in human disease.

Another investigation during the past year has shown that white cells called B-lymphocytes can produce a substance that kills fibroblast cells which produce the important collagen fibers of the periodontal tissues. The B-lymphocytes are abundant in severely inflamed periodontal tissues. This destruction of fibroblasts is thought to decrease the formation of new collagen (fibrous tissue). Related studies showed that specimens of diseased human gingiva (gums) produced 25-35% less collagen than specimens of healthy tissues. Other studies of the collagen-destroying enzyme called collagenase proved that the enzyme exists in human gingiva in an inactive form, which can be activated with substances obtained from inflammatory cells (lymphocytes). Thus, the net loss of collagen (fibrous tissue) observed in periodontal disease is probably due to both decreased production and increased destruction.

An ongoing clinical study has shown that treatment of advanced cases of severe periodontal disease with tetracycline antibiotic, 1 gram per day for 21 days every 6 months, has prevented further damage for 3 years.

A four-year study in beagle dogs showed that gingivitis (gum inflammation) and destructive periodontal disease with bone loss could be controlled by meticulous daily tooth brushing. Dogs that did not receive toothbrushing showed periodontal bone loss averaging nearly 4 mm during the period. This study indicates that destructive periodontal diseases can be prevented by daily mechanical oral hygiene.

In February 1975, NIDR began a formal evaluation of its periodontal disease research activity, including both extramural and intramural endeavors. Inasmuch as this is the first comprehensive evaluation of an NIDR research program, it will be approacned 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 evaluation has been completed. The panel report is being prepared and will be submitted to the Institute Director in January, 1976.

Restorative Materials

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
	Amount	Amount	Amount	Amount
Restorative Materials...	$2,651,000	$3,060,000	$3,025,000	-$35,000
Budget Mechanism:				
Research Grants				
Regular				
Noncompeting.....	$1,550,000	$1,550,000	$1,901,000	+$351,000
Competing.....	157,000	566,000	332,000	-234,000
Special.....	46,000	46,000	47,000	+1,000
Training Programs				
Training Grants.....	469,000	469,000	325,000	-144,000
Fellowships.....	29,000	29,000	20,000	-9,000
Research and Development				
Contracts.....	400,000	400,000	400,000	0
Total.....	2,651,000	3,060,000	3,025,000	-35,000

Objectives, 1977:

Nearly every person will require some kind of oral-facial restorative procedure during his lifetime to replace missing and damaged tissues resulting from oral-facial diseases and injuries. Repairing the damage caused by decay, periodontal (gum) disease, congenital malformations, oral cancer, accidents, requires durable, easily applied materials and techniques. Until there is sufficient knowledge to completely prevent oral-facial diseases and disorders, there will be a need for research to develop improved materials and devices.

Currently, the Program is concerned with six major areas: (1) filling materials, including silver amalgam alloys and the new composites for repairing damaged teeth; (2) bonding agents, including adhesive coatings and cements for preventing decay on the chewing surfaces of teeth and for sealing the margins of fillings; (3) maxillofacial appliances for replacing tissue defects resulting from congenital abnormalities, cancer or accidents; (4) artificial tooth implants to substitute for missing teeth and to serve as anchors for bridges and dentures; (5) endodontic and pulp studies; (6) studies on equipment and devices designed to improve dental care.

Continued research on amalgams, will include basic metallurgical studies and clinical evaluation of the newer less corrodible amalgams.

Continuing investigations of tooth implants will involve both animal and in vitro studies of materials and designs. Results of long-term animal studies expected during Fiscal Year 1977 may lead to clinical trials.

The increasing price of gold and the possible effect this may have on its use in dental prosthetics is of growing concern to the dental community. The Program intends to pursue ways to increase the use of non-precious metals.

The Program will also attempt to stimulate studies on diseased dental pulp and on the development of improved root canal instruments and therapy.

Accomplishments, 1976:

In amalgam fillings, hard silver-tin alloy particles are bound together in a matrix composed of a fine grained silver-mercury phase and a weak tin-mercury phase. The tin-mercury phase is believed to cause breakdown of amalgam fillings because it corrodes easily and has low tensile strength. As a result of basic metallurgical research supported by NIDR, it is now possible to restore teeth with amalgam alloys which do not contain the weak tin-mercury phase. Several such amalgams are currently being tested clinically on a modest scale.

All of the composite filling materials currently on the market are based upon NIDR supported research. Since these resins are aesthetically more pleasing than amalgam, they are used for restoring front teeth. However, they do not, as yet, have sufficient mechanical strength for use on chewing surfaces of molar teeth. In current investigations attempts are being made to increase the mechanical strength and longevity of these composite resins so that they can also be used for posterior restorations. Recent clinical evaluations show that composite fillings maintained their color match, marginal integrity and overall shape for a period of three years.

The Program strongly supports research on tooth implants. Promising candidate material for implants include chromium-cobalt alloys, titanium, ceramic materials including glass and alumina, and yitreous carbon. At present experimental implant materials in various shapes are being inserted into the jaws of animals (dogs and baboons) for long term trial. In one of these preclinical studies, free standing cylindrical titanium implants in baboons have survived 30 months. In another study, microscopic observations indicated that bioglass ceramic material shaped like a natural tooth and inserted into the jaws of baboons is highly compatible with adjacent oral tissues. This material may find wide use for medical implant devices especially in the orthopedic and craniofacial fields.

The Program also sponsored a national symposium on procedures by which dentists prepare teeth for restorations. In performing these procedures, dentists must surgically remove part of the hard structure of teeth by drilling and cutting. The methods they use must satisfy the rigid demands of safety, efficiency, precision, and minimum pain. To draw upon knowledge from a variety of industrial and scientific fields, the symposium, "Promoting New Basic Research on Cutting in Dentistry," was held at the annual meeting of the American Association for the Advancement of Science. It brought together experts who understand the science of what happens when a moving instrument comes into contact with a hard material of a different nature. Special attention was given to drilling and cutting methods used in industry. The meeting set the stage for further exploration of new and improved cutting techniques for dentistry.

The rapid advances in biomedical engineering have not been applied in the preventive, diagnostic or therapeutic areas of dentistry apparently because biomedical engineers and dentists have not communicated. To foster needed communication the Program brought together biomedical engineering and oral-medical scientists in a successful planning session to discuss how NIDR might help these two groups collaborate. As a result, a workshop on this subject is scheduled for February, 1976.

Craniofacial Anomalies

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Craniofacial Anomalies	$6,746,000	$7,397,000	$7,072,000	-$325,000
Budget Mechanism:				
Research Grants				
Regular				
Noncompeting.....	$3,995,000	$3,995,000	$4,666,000	+$671,000
Competing.....	320,000	971,000	621,000	-350,000
Special.....	454,000	454,000	456,000	+2,000
Training Programs				
Training Grants.....	602,000	602,000	311,000	-291,000
Fellowships.....	1,075,000	1,075,000	418,000	-657,000
Research and Development				
Contracts.....	300,000	300,000	600,000	+300,000
Total	6,746,000	7,397,000	7,072,000	-325,000

Objectives, 1977:

The Craniofacial Anomalies Program Branch supports research on cleft lip/palate, other congenital anomalies, malocclusion, and acquired deformities of the face and jaws. Each year clefting of the face and mouth afflicts 6,000 newborns and another 1,200 newborns have other severe deformities that were untreatable until recently. As a result, the number of severely deformed patients still untreated has increased to approximately 20,000. Three of every four children in the United States develop malocclusion (their teeth are crooked or their jaws do not fit together properly when they bite). In half of these, the malocclusion is a severe handicap. Approximately 1.4 million children born in 1974 will become handicapped in this way. In addition, thousands of craniofacial deformities are acquired each year through surgery and accidents. The annual costs for treating craniofacially deformed individuals exceeds one billion dollars.

Basic studies of clefts of the face and mouth and of other syndromes will attempt to discover how hereditary mechanisms are involved in the development of the deformities. Studies in animals showed that certain agents cause craniofacial deformities by affecting a certain gene on a specific chromosome, and early studies suggest that the same mechanisms may operate in humans. So far investigators have detected specific hereditary proteins on human cell surfaces, and subsequent studies are expected to show how the interactions between toxic chemicals and these surface proteins bring about defects.

In studies planned scientists will trace the development of embryonic cells into the specialized tissues of the face and mouth. Expanded studies will also be made of the signals by which these cells communicate with each other and with their environment so that investigators can pin point the events which lead to abnormal development. Since cleft lip occurs more frequently in families in which an offspring already has cleft palate, such families will be studied to search for environmental and maternal factors which may produce clefts. Other clinical research will be concerned with helping victims of craniofacial anomalies establish themselves as useful members of society after they have undergone surgery. The recent dramatic successes achieved by surgical treatment of severe craniofacial deformities promises many of these individuals a normal life. While surgery corrects visible physical defects, it is now necessary to

show what effects the surgical and healing processes have on normal facial growth and on the maturation of the individual. Research programs on surgery, wound healing, facial growth and psychosocial development will be conducted.

In studies related to orthodontics, scientists will attempt to improve the means for predicting individual growth patterns by studying the hereditary aspects and the chemical and mechanical principles involved in the growth of the face and skull. Such studies will examine bone enlargement, muscle changes, and collagen (fibrous tissue) alterations. Specific studies will be made of chemical and mechanical factors which come into play when teeth erupt, when bone or tooth roots resorb (melt away), when teeth are moved orthodontically and when bony sutures (seams) enlarge.

Accomplishments, 1976:

Research supported by the NIDR has improved surgical treatment of cleft lip/palate and associated nose defects and reduced the number of operations in each patient to one-half of those required previously. Past research has also made possible the early diagnosis and correction of speech problems in cleft palate children. The identification of patients who need extended treatment of their palatal cleft can now be done in 95% of patients by age 7 years.

Since conventional cleft palate surgery has caused retarded growth of the upper jaw, researchers conducted basic studies in animals to test new methods of surgery and postoperative tissue management. These studies showed that growth was not retarded when the new techniques were used.

Recent studies in animal models indicated that certain anticonvulsants and tranquilizers may cause cleft palate by reducing neuromuscular activity in the mouth and throat. Other studies suggested that environmental agents may cause cleft palate by interacting with specific cell surface chemicals in individuals with a certain genetic background. One study of this type showed that cortisone caused cleft palate by interacting with cell surface glycoproteins under the control of a specific genetic site on a chromosome. This heritable trait is not present in all strains of animals. In an outstanding breakthrough, it was shown that achondroplastic dwarfism is linked to defective function of a single enzyme in both humans and animals. Apert's syndrome, a condition in which the bones of the skull stop growing at an early age, has been associated with increased paternal age at conception and with increased risk of congenital heart disease.

In studies related to orthodontics it was shown that localized forces produce a definite pattern of biochemical changes in bone and that prolonged forces on the upper jaw will cause bone resorption at all bone sutures (seams) around the jaw. This latter finding suggests that the structure of the face can be changed to a more desirable shape.

Pain Control and Behavioral Studies

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Pain Control and Behavioral Studies....	$1,659,000	$1,840,000	$1,554,000	-$286,000
Budget Mechanism:				
Research Grants				
Regular				
Noncompeting.....	$687,000	$687,000	$812,000	+$125,000
Competing.....	212,000	393,000	352,000	-41,000
Special.....	65,000	65,000	67,000	+2,000
Training Programs				
Training Grants.....	487,000	487,000	126,000	-361,000
Fellowships.....	108,000	108,000	97,000	-11,000
Research and Development				
Contracts.....	100,000	100,000	100,000	0
Total.....	1,659,000	1,840,000	1,554,000	-286,000

Objectives, 1977:

Pain has always been a major problem. It ranks as perhaps the most common disabling condition of man. Its economic and psychological costs are incalculable; estimates of working days lost each year in the United States run into the multimillions. Pain itself is the most common symptom which impels people to seek professional treatment. The pain problems which concern the National Institute of Dental Research are: the pain occurring directly in dental and oral tissues; painful oral-facial conditions such as tic douloureux and myofascial pain dysfunction; and the fear and anxiety syndrome evoked by the prospect of dental treatment, a syndrome which keeps millions from seeking dental care. Since the underlying mechanisms involved in pain are not understood, effective control of painful conditions has been severely hampered. Recently, however, there has been a resurgence of interest in pain research. The NIDR has contributed significantly to this resurgence.

There is also a serious deficiency in knowledge of the behavioral aspects of disease prevention and control. While it is clear that programs to motivate individuals to prevent dental caries and periodontal disease would greatly improve oral health, there is little scientific base to initiate such programs. Thus, the Pain Control and Behavioral Studies Program fosters research to increase basic and applied knowledge of pain and the fear of pain and to gain a deeper understanding of psychological responses to dental problems.

During FY 77 emphasis will be given to a number of specific areas. Working with the International Association for the Study of Pain, NIDR will improve classification systems and develop standardized terminology for the diagnosis, evaluation and treatment of oral-facial pain conditions. In cooperation with the American Dental Association and the American Association for Dental Schools, NIDR will establish pain control research and training centers in dental schools. These centers will improve the management of dental patients with pain problems.

A better understanding of acupuncture is required before its proper place in dental anesthesia and pain control can be determined. Research to achieve this understanding will be pursued. Attempts will be made to increase our knowledge of the total spectrum of pain control methods used in dental practice. These include local and general anesthetics, which need investigation

individually as well as in combination with other drugs having amnesic, tranquilizing and sedative effects. Finally, basic studies on a variety of behavioral problems relevant to oral-facial conditions and diseases will continue.

Accomplishments, 1976:

Research supported by the Pain Control and Behavioral Studies Program increased sharply during FY '76. Among new projects initiated were major studies of the fear and anxiety syndrome that keeps millions of Americans from seeking dental treatment. These studies will provide a better understanding of the nature of this fear and anxiety response and will develop means to alleviate the condition. Highlights from research projects currently being supported are outlined in the following paragraphs.

Studies of the pain associated with the temporomandibular joint (TMJ), the hinge joint of the jaws, has focused on the psychological factors involved. In these studies it was shown that placebo (mock) treatment gave relief to 64% of 25 patients. The placebo treatment consisted of light grinding on uninvolved teeth. It was also shown that limited psychotherapy produced complete remission of symptoms in 65% of 23 patients. In a long-term study involving 100 patients, conservative treatment consisting of mild drugs, psychotherapy and placebo tooth grinding maintained relief in 94% of these patients for as long as eight years after therapy. This result indicates that commonly used radical approaches consisting of surgery, local injections, strong drug therapy, and extensive tooth grinding, are unnecessary. It was also demonstrated in patients with TMJ problems that the masseter muscle, the main jaw muscle, responds strongly to stress. This finding suggests that jaw muscles may serve as target organs for stress in certain patients.

Acupuncture is being evaluated not only as a treatment for dental and oral-facial pain, but also as an experimental tool to study the basic aspects of the pain. In studies involving 73 subjects and 369 experimental trials, acupuncture relieved experimentally-induced pain. Scientists are now attempting to separate the psychologic from the non-psychologic components of this pain relief. In another project, a study of individual operator variables encountered in the practice of acupuncture demonstrated that:

1. Each of eight acupuncturists was able to prolong pain tolerance;
2. The success achieved by the different acupuncturists varied;
3. The acupuncture analgesic effect was greater for moderately distressing pain than for high levels of pain.

In a highly significant study, it was shown that objective, measurable, electrical activity could be observed in the brain at the moment individuals began to perceive acute pain in the teeth. This is the first time that objective signs have been clearly linked to subjective symptoms of pain.

Soft Tissue Stomatology and Nutrition

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Soft Tissue Stomatology and Nutrition.....	$2,949,000	$3,225,000	$3,200,000	-$25,000
Budget Mechanism:				
Research Grants				
Regular				
Noncompeting.....	$1,505,000	$1,505,000	$1,728,000	+$223,000
Competing.....	200,000	476,000	250,000	-226,000
Special.....	206,000	206,000	201,000	-5,000
Training Programs				
Training Grants.....	160,000	160,000	160,000	0
Fellowships.....	538,000	538,000	482,000	-56,000
Research and Development				
Contracts.....	340,000	340,000	379,000	+39,000
Total.....	$2,949,000	$3,225,000	$3,200,000	-$25,000

Objectives, 1977:

The Soft Tissue Stomatology and Nutrition Program supports research in oral soft tissue diseases, salivary secretions, nutrition and mineralization. Oral soft tissue diseases, including fever blisters, canker sores, and oral cancer, create health problems for millions of people. Fever blisters are caused by herpes simplex virus which can also cause blindness and may be related to cancer. Normal salivary secretions and adequate systemic nutrition are both essential for the growth and maintenance of healthy oral tissues. In addition, the process of mineralization is important because the mouth contains calcified structures.

Soft Tissue Diseases:

It is estimated that over 25% of the population suffers from oral soft tissue disorders and more than 50% have recurrent oral lesions (sores). Current herpes virus studies are designed to learn more about the immunologic aspects of the disease, to discover why the virus localizes in particular tissues and what reactivates it, to test antiviral drugs, and to develop a vaccine. The purposes of the studies on canker sores (recurrent aphthous ulcers) are to develop basic and clinical knowledge of this condition and associated syndromes. Premalignant lesions will be studied to discover the metabolic changes which lead to malignancy. The role of cancer causing agents will also be assessed.

Nutrition:

Grants and contracts will be employed to study the effect of poor nutrition on salivary glands and other orofacial structures. The effect of protein/calorie deficiency on oral mucous membrane integrity, permeability and metabolism will also be studied. Attempts will be made to develop balanced diets which contain the appropriate content of nutrients, (including trace elements) with a minimum of detrimental ingredients, such as sucrose. A major objective will be to increase postdoctoral training awards in nutrition.

Salivary Glands and Their Secretions:

Saliva moistens food for swallowing and protects the soft and hard oral tissues by serving as a lubricant, a neutralizing fluid, a physical barrier, and as an antibacterial agent. Basic studies will emphasize the biochemistry of salivary gland growth and function. Attempts will also be made to expand training in the salivary gland field.

Accomplishments 1976:

In studies of herpes simplex virus infections, it was shown that this virus depresses the host white qell response and apparently makes it difficult for the infected individuals to rid themselves of the virus. As a result, the herpes simplex virus remains hidden in the tissues and causes persistent or recurrent infections. In other studies scientists first made hamster cells tumorous by exposing them to inactivated oral herpes virus and showed that the hamster tumor cells each contained herpes virus protein on the cell surfaces. These findings may be highly important in determining the relationship of oral viruses to cancer and in developing an anti-herpes vaccine.

Nutrition:

The capacity of oral mucous membranes to serve as a barrier against microorganisms or their toxins is important in periodontal disease, aphthous ulcers and other diseases. In studies of animal tissues, both protein deficiency and inadequate Vitamin C were shown to decrease the barrier capacity of these membranes against bacterial endotoxins. Scientists also confirmed earlier studies which indicated that protein deficiency only during gestation and lactation causes growth stunting in rat pups as well as increased dental caries. The caries susceptibility in these experiments may be related to defective teeth or salivary gland function. Results to date show that the malnourished animals produce less saliva which is low in protein.

Salivary Glands and Their Secretions:

In a study on the regulation of salivary gland function, it was found that certain pharmacologic agents caused drastic changes in gland function and in the content of the secretions. In another study scientists discovered several unique salivary proteins.

Mineralization:

The collagen (a fibrous protein) of the mineralizing tissue dentin was shown to contain a unique distribution of cross links.

Dental Research Institutes

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Dental Research Institutes.....	$7,200,000	$7,200,000	$7,200,000	0
Budget Mechanism: Research Grants Special.....	$7,200,000	$7,200,000	$7,200,000	0
Total.....	7,200,000	7,200,000	7,200,000	0

Objectives, 1977:

Dental Research Institutes/Centers were initiated in 1967 to provide a strong stimulus to dental research, beyond anything which could reasonably be expected through use of the conventional grant mechanisms being employed at that time. Concentrating the resources and efforts of a few universities and NIDR has made it possible to establish ideal environments which have attracted high quality scientists from many different disciplines to work as interdisciplinary teams on dental problems. As anticipated, these scientists have interacted with existing dental investigators and clinicians, as well as with members of traditional basic science departments to derive the greatest possible benefit from existing dental research capability and other institutional research strengths. This new approach to oral health research has enlisted the collaboration of all appropriate elements of the university. During the past eight years the five Dental Research Institutes/Centers have established strong interdisciplinary research programs in the fundamental biomedical sciences and now stand ready to expand clinical investigations.

In 1977 these five Institutes/Centers will continue to be supported and efforts will be directed toward extension of existing laboratory projects into clinical areas wherever feasible. The Institutes will be encouraged to capitalize upon opportunities to initiate new clinical investigations. Emphasis will also be placed upon activities related to the dissemination of research findings to practitioners and the public as well as to the scientific community. In addition to the usual routes of scientific communication such as teaching, publication and presentation of papers, seminars and workshops, the Institutes will be encouraged to reach a much broader audience through the use of newsletters and other lay publications, participation in meetings involving practitioners and lay members of the public, and other mechanisms which are deemed appropriate to the purpose. Investigators in the Institutes will seek additional sources of research support in order to make Institute funds available for these 1977 objectives.

Accomplishments, 1976:

The NIDR supported five Dental Research Institutes/Centers at the Universities of Alabama, Michigan, North Carolina, Pennsylvania, and Washington during this year. Specific research accomplishments are included in the reports of the categorical programs.

The Institute of Dental Research at the University of Alabama continued its well-established research program with four interdisciplinary groups conducting studies of: (1) dental caries, (2) connective tissues, (3) mineralization, (4) periodontal disease. More than 100 scientific papers were published in the past year. Plans were initiated to develop a clinical investigation unit at the

Veterans Administration Hospital in Birmingham. These plans call for the staff of the clinical investigations unit to be integrated with the staff of the Institute of Dental Research and the School of Dentistry.

The Dental Research Institute at the University of Michigan is organized according to three major research targets; (1) periodontal disease and caries, (2) viral disease in the oral cavity, (3) development and function of masticatory apparatus. Over 100 scientific publications were produced during the year.

The Center for Oral Health Research at the University of Pennsylvania conducted studies in the following areas: (1) molecular structure of oral tissues, (2) molecular biology of oral bacteria, (3) immunobiology of the oral cavity, (4) replication of herpes simplex virus, (5) periodontal tissues and dental plaque, (6) interaction of oral bacteria and inflammatory cells, (7) physical and life science studies of dental sealants and orthodontic direct bonding. Approximately 60 papers were published as a result of this work. The Director has instituted a positive effort to bring basic and clinical scientists together to work on problems of common interest.

At the University of North Carolina the Dental Research Center has six research teams at work in the following areas: (1) neural mechanisms, (2) growth mechanisms, (3) mineralization mechanisms, (4) immunological mechanisms, (5) hemostasis mechanisms, (6) biomaterials. More than 150 scientific papers were published by these groups in the last year. A new Director has been appointed and a new Dean with a strong research orientation is heading the dental school. It is anticipated that these two appointments will facilitate the development of clinical investigations in this center.

The Center for Research in Oral Biology at the University of Washington focuses its research in three areas: (1) periodontal disease, (2) salivary secretions, (3) nutrition. Approximately 70 publications were produced by the Center last year. The Director of the Center and the leader of the nutrition group both left the University for other positions this year. The Vice President for Health Affairs has appointed a committee to review the past accomplishments of the Center and to make recommendations with regard to its future direction before seeking a new Director. The NIDR staff will meet with this committee and provide some guidance to assure that its recommendations do not conflict with NIDR's needs and the purposes of the grant.

Intramural Research and Direct Operations

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
	Amount	Amount	Amount	Amount
Intramural Research and Direct Operations	$10,534,000	$10,534,000	$11,741,000	+$1,207,000
Positions	205	212	205	-7

Objectives, 1977:

The Institute's laboratory and clinical research studies are directed toward a better understanding of the causes of dental and oral-facial diseases and disorders and the development of treatment, control, and preventive measures. Emphasis is also placed on oral-facial pain and its control.

As part of a multi-pronged effort to reduce the incidence of dental caries (tooth decay), the microbial causes of this disease will continue to receive attention. To lay a foundation for the development of preventive measures, studies will seek needed information about the individual bacterial species involved, events that lead to their colonization of the tooth surface, and the biochemical and genetic qualities that enable them to survive in the mouth.

Increased emphasis will be placed on furthering understanding of the mechanisms of initiation and progression of certain inflammatory oral disorders, notably periodontal disease. More extensive efforts will be made to document microbial and immunological mechanisms in periodontal disease, and to develop measures, such as vaccines or anti-inflammatory or antimicrobial drugs, to counter the destructive processes. Genetic susceptibility is also being explored.

Studies of disordered anatomical development continue to focus on such anomalies as cleft lip and palate, with emphasis on environmental and genetic factors. At the cellular level, factors that control the behavior of developing cells will be examined.

Another inquiry will explore sensory and motor reflexes and performances of the mouth and face, especially of feeding and speech in the early years. Adult performance, such as caries-inducing eating patterns, build upon infant and childhood sensory experiences as well as upon developmental changes in the brain.

Substantive research continues to be directed to oral and facial pain. Laboratory and clinical studies will be undertaken to define and clarify pain mechanisms, develop reliable methods of measuring the acute and chronic oral-facial pain in humans, and determine effective means of controlling pain. Pain pathways and the efficacy of various pain-relieving drugs and other agents will be studied in animal models. In humans, effective evaluation of new pain control agents must await the development of a reliable, quantitative pain index. Once this index is available, non-pharmacologic methods, such as electroanalgesia, biofeedback, acupuncture, and behavioral modification, will be studied in addition to new drugs. Another area of emphasis is the physiological and behavioral effects of new short-acting sedatives used for controlling anxiety and apprehension in ambulatory dental patients.

A better grasp of the full potential of the herpes simplex virus for injury may be expected, building on significant new findings on how this virus persists in the body. Attempts will be made to establish animal models to determine if other ulcerative conditions of the skin and gastrointestinal tract, such as peptic ulcers and colitis, might be due to latent viruses harbored in nearby nerve centers. Parallel efforts will be made to recover viruses from patients

with such diseases. The possibility that damage to specific nerve centers may trigger reactivation of viruses will also be examined. This might demonstrate that trigeminal neuralgia, Shy-Dragger syndrome, and other unusual types of facial pain have a viral origin triggered by nerve injury. In addition, work will continue on the development of a herpes virus vaccine against different strains of the virus in animals.

In another area of virology, it is planned to search for viruses in the salivary glands and saliva of patients with pancreatic disease (e.g., tumors, acute pancreatitis, diabetes) and salivary gland diseases. Efforts will also be made to determine whether cytomegalovirus (a member of the herpes group) can be identified with malignant and nonmalignant diseases of the salivary gland. Among other related activities, studies on genetic control of animal diabetes induced by viruses will continue.

Recognition and analysis of specific factors that hinder interpretation of X-ray pictures is necessary before clinicians can expect to detect and treat both tooth decay and periodontal disease in their early stages before the damage becomes irreversible. Models of experimental X-ray systems will be studied to determine the quantity and quality of information that may be expected in a specific diagnostic situation. Data from these models should provide rational bases for developing better methods of diagnosis.

Other direct operations supports the Director and his immediate staff concerned with administrative management, scientific and health reporting, financial management, program planning and evaluation, and computer processing services related to the Institute's overall activities.

Accomplishments, 1976:

The following are illustrative of the accomplishments in laboratory and clinical research covering a broad range of dental sciences.

Clear-cut evidence has emerged that periodontal disease is caused by self-destructive immune reactions to bacteria and other substances in the film of dental plaque found on teeth. Some reactions involve white blood cells, while others involve interactions with complement enzymes in the blood. These reactions are responsible for painfully inflamed gum tissues and the wasting of bone that culminates in the loss of sound teeth in adults.

Significant strides were made in the study of herpes simplex virus through the establishment of an animal model system. This system provides an unparalleled opportunity to study the factors responsible for reactivation of herpes, viral reservoirs, and the effectiveness of immunization and drug therapy in preventing and treating herpetic eruptions. Attempts to immunize mice have demonstrated that latent infections can be prevented in up to 90 percent of the animals infected with one strain of the virus. Further work is needed to determine the protection afforded by different strains of the herpes simplex virus, the usefulness of inactivated versus live virus, and the potential danger of vaccines to man.

Advances were also made in continuing research on events in the growth and development of oral-facial tissues. Studies have clarified the formative sequence of the secondary palate and how certain drugs cause cleft palate in animals. Molecular defects in collagen assembly have been identified in patients with some types of Ehlers-Danlos syndrome. In addition, the chemical signals that alert white blood cells to detect and approach invading bacteria have been identified, and synthetically produced material is being tested for efficiency.

Program Management

	1976 Revised President's Budget Amount	1976 Appro-priation Amount	1977 Estimate Amount	Increase or Decrease Amount
Program Management.....	$1,389,000	$1,982,000	$2,101,000	+$119,000
Positions.....	30	31	30	-1

Objectives, 1977:

In FY 1977, this activity will continue to provide for the overall administration, direction, and coordination of the Institute's grant and contract programs.

Institute review and approval activities include the Associate Director for Extramural Programs, a Deputy Associate Director, an assistant for special programs, 14 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 1977 budget includes 480 research grant, fellowship and training awards, totaling in excess of 31 million dollars that will have to be processed by this staff.

Collaborative research includes an Associate Director, 3 contract specialists, a staff assistant, and clerical support for personnel responsible for development, implementation, and evaluation of research and development contracts and caries, periodontal diseases, restorative materials, craniofacial anomalies, soft tissue stomatology, and pain control and behavioral studies. The 1977 budget includes 70 research and development contracts costing $5,408,000. Much of the increase for this activity in this budget request is required for mandatory items and an increase of this Institute's proportionate share of increase costs of centrally furnished services.

Accomplishments, 1976:

The staff supported by this activity continued to provide scientific and administrative management for the Institute's grant and contract programs. The 1976 workload included the processing of approximately 496 research grants, special awards, training and fellowship applications totaling in excess of 32 million dollars, and 87 contracts and agreements for a total amount of $4,575,000.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Caries. (Public Health Service Act, Title IV, Part C)

1976 Estimate			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
39	$9,717,000	Indefinite	34	$9,879,000

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 1976: 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 81 research grants, 5 career awards, 7 fellowships, 1 training grants, and 40 research and development contracts will be supported in 1976.

Objectives for 1977: Research will continue within the broad framework of the four major program objectives. Some specific objectives for 1977 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 84 research grants, 5 career awards, 5 fellowships, 1 training grant and 42 research and development contracts will be supported in 1977.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Periodontal Diseases. (Public Health Service Act, Title IV, Part C)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$6,435,000	Indefinite	---	$6,472,000

Purpose: The goal of the Periodontal Diseases Program Branch is to develop new knowledge that will lead to the eradication of periodontal diseases.

Explanation: Branch research programs are carried out by support of grants, contracts, training grants, fellowships, and career awards.

Accomplishments in 1976: New studies corroborated previous findings that specific bacteria are associated with different forms of human periodontal (gum) disease. During FY 76 seven different types of these organisms were shown to cause periodontal disease in otherwise germ-free animals. Other studies showed that bacterial poisons known as endotoxins become absorbed to human tooth roots during disease. These endotoxins may prevent the reattachment of healthy gum cells when the tissues are healing after treatment. Animal experiments also indicated that chemicals released when gum tissues are inflamed could not only break down existing collagen protein that gives fibrous tissue its strength, but could also inhibit the formation of new collagen. Clinical studies showed that periodontal diseases could be controlled by antibiotics and/or regular and thorough mechanical hygiene such as toothbrushing.

Support in FY 1976 will include approximately 79 regular research grants, 9 contracts, 7 training grants, 25 fellowship awards and 3 career awards.

Objectives for 1977: Investigators will attempt to prevent and control periodontal diseases through studies of all the steps in the disease process from the time that bacteria first begin to grow on tooth surfaces to the ultimate destruction of all the periodontal tissues. The recently identified disease-causing bacteria will be thoroughly characterized so that it will be possible to test specific immunization procedures in animals. Studies of drugs and chemicals likely to prevent the attachment and growth of bacteria on tooth surfaces will be further expanded and promising treatments for the type of periodontal disease that causes rapid bone destruction in adolescents will be supported.

Approximately 89 research grants, 3 career awards, 13 fellowships, 3 training grants, and 10 contracts will be supported in 1977.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Restorative Materials. (Public Health Service Act, Title IV, Part C)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$3,060,000	Indefinite	---	$3,025,000

Purpose: This Program area is concerned with providing the best restorative materials that research can provide to repair the ravages of dental disease and deformities.

Explanation: This activity is carried out by the support of research grants and contracts, graduate training grants, fellowships and research carcer awards.

Accomplishments in 1976: Interim results of long term animal studies indicated that tooth implants made of titanium or bioglass ceramic are highly promising. Long term clinical evaluation of newly developed silver amalgam filling materials were initiated this fiscal year.

Approximately 50 research grants, 2 career awards, 1 fellowship, 7 training grants, and 5 research and development contracts will be supported in 1976.

Objectives for 1977: Results from clinical evaluations of several materials and designs of tooth implants should become available in Fiscal Year 1977. Continued efforts in clinical evaluations will be pursued in the areas of amalgams, composite resins, and precious and non-precious metals.

Approximately 58 research grants, 2 career awards, 1 fellowship, 4 training grants, and 5 research and development contracts will be supported in 1977.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Craniofacial Anomalies. (Public Health Service Act, Title IV, Part C)

1976 Estimate		1977	Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$7,397,000	Indefinite	---	$7,072,000

Purpose: The goal of the Craniofacial Anomalies Program Branch is to develop new knowledge that will reduce the incidence, morbidity and mortality of craniofacial anomalies.

Explanation: Branch research programs are carried out by support of grants, contracts, training grants, fellowships, and career awards.

Accomplishments in 1976: Research supported by the NIDR has improved surgical treatment of cleft lip and palate. Diagnosis and correction of cleft lip and palate can now be done earlier than before. As a result of animal studies on new surgical procedures, it may soon be possible to avoid the retarded growth of the upper jaw which has often followed conventional cleft palate surgery. These new methods are now ready to be tested in humans. Specialized animal and tissue culture studies have provided information on normal and abnormal development and have implicated factors that may cause clefts. These factors include certain drugs that inhibit muscular movements of the tongue and palate and a heritable trait involving cell-surface proteins that make the experimental animal susceptible to cortisone-induced cleft palate. Other studies have linked achondroplasia, a common form of dwarfism, with a defective enzyme. It has also been found that children born with Apert's syndrome, a condition in which bones stop growing prematurely, have older fathers. Research on malocclusion has demonstrated that the bone structure of the face and jaws may be remodeled by application of localized forces. The face can in this way be changed to a more desirable shape.

Support in 1976 will include approximately 72 regular research grants, 3 contracts, 10 training grants, 26 fellowships, 4 career awards, and 1 specialized center.

Objectives for 1977: Investigators will continue to develop knowledge leading to an understanding of the cause of human craniofacial deformities. This will be accomplished through expanded studies of normal and abnormal development in animal embryos and in cell and tissue cultures. Substances such as drugs that have a demonstrated or suspected effect on embryological development will be tested in these models. Research to determine how hereditary factors interact with such environmental factors to produce deformities will continue to receive emphasis. New clinical studies will attempt to discover environmental and metabolic factors that may cause craniofacial deformities.

Approximately 75 research grants, 4 career awards, 9 fellowships, 4 training grants, 6 contracts, and 1 specialized center will be supported in 1977.

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, Part C)

1976 Estimate		1977	Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,840,000	Indefinite	---	$1,554,000

Purpose: This Program functions to increase knowledge of the basic and applied aspects of dental and oral-facial pain problems so that the suffering associated with these conditions can be more effectively dealt with; a second purpose is to increase understanding of the behavioral aspects of dental problems to develop more effective means of dealing with these problems.

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 1976: It has been demonstrated, for the first time, that acute experimental pain in humans can be directly related to objective measurements of electrical activity in the brain. This finding will provide a new approach to correlating the objective and subjective factors involved in the human pain experience. Acupuncture was shown to reduce experimental pain. Individual acupuncturists showed clear-cut differences in their ability to successfully reduce pain. An eight-year study showed that pain associated with the hinge-joint of the jaws could be relieved by conservative treatment which included psychotherapy.

Approximately 28 research grants, 3 career awards, 3 fellowships, 7 training grants, and 1 research and development contract will be supported in 1976.

Objectives for 1977: Continuing efforts will be made to develop and support quality research and training in the many problem areas relevant to oral-facial pain and dentally-related behavior. The project to improve pain classification systems and to develop a standard terminology will continue. Working cooperatively with the American Dental Association and the American Association of Dental Schools, NIDR will continue its efforts to establish pain-research centers in selected dental schools to upgrade dental education, research and treatment in this important area. The multidisciplinary approach to pain research will continue to be emphasized in Program development.

Approximately 33 research grants, 3 career awards, 3 fellowships, 2 training grants, and 1 research and development contract will be supported in 1977.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Soft Tissue Stomatology and Nutrition Program Branch. (Public Health Service Act, Title IV, Part C)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$3,225,000	Indefinite	---	$3,200,000

Purpose: The purpose of this Program is to develop knowledge in four areas of research: soft tissue diseases, nutrition, salivary glands and their secretions, and mineralization.

Explanation: The activities of this Program are carried out by support of research grants, research contracts, graduate training grants, fellowships, and research career awards.

Accomplishments in 1976: Studies of herpes simplex virus (the virus of fever blisters) indicated that this virus depresses the white blood cell response of infected individuals and may make it difficult for these individuals to rid themselves of the virus, thus accounting for the persistent and recurrent infections this virus causes. Nutritional studies indicate that both protein deficiency and inadequate vitamin C cause oral mucous membranes to be more permeable to bacterial endotoxin. Studies of saliva have identified new proteins which may contribute to dental plaque formation, to the remineralization of early carious lesions, or to antibacterial activity.

Approximately 31 research grants, 8 career awards, 13 fellowships, 2 training grants, and 5 research and development awards will be supported in FY 1976.

Objectives for 1977: Herpes virus studies will emphasize immunology, tissue localization and reactivation of the virus, antiviral drugs, and vaccine development. Studies on recurrent aphthous ulcers (canker sores) are intended to develop basic and clinical knowledge which will lead to new treatment and preventive programs. Nutrition studies will seek better methods of managing oral conditions aggravated by inappropriate diets and better methods of assessing nutritional problems in all age groups. Studies on the quality of modern foods will attempt to develop diets of balanced composition which contain the appropriate content of essential nutrients, including trace elements, and a minimum content of detrimental ingredients, such as sucrose. New knowledge generated in these studies will be brought to the attention of the scientific and clinical communities. The Program will also support research on salivary gland physiology and biochemistry in health and disease.

Approximately 38 research grants, 8 career awards, 10 fellowships, 2 training grants, and 6 research and development awards will be supported in 1977.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$7,200,000	Indefinite	---	$7,200,000

Purpose: The major objective of Dental Research Institutes/Centers is to broaden and strengthen the scientific base underlying the national capability to improve oral health.

Explanation: The programs of this activity are supported by research grants.

Accomplishments in 1976: Five Dental Research Institutes/Centers received continued support. Interdisciplinary research teams conducted studies covering the entire range of oral health problems, producing almost 500 scientific publications.

Objectives for 1977: Continued support will be provided for the five Institute/Centers. Emphasis will be placed upon the development of clinical investigations and upon the dissemination of research findings to practitioners and the public.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Intramural Research and Direct Operations. (Public Health Service Act, Title IV, Part C)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
212	$10,534,000	Indefinite	205	$11,741,000

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. Other direct operations support the Director and his immediate staff concerned with overall Institute administrative activities.

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 1976: Clear-cut evidence has emerged that periodontal disease is caused by self-destructive immune reactions to bacteria and other substances in the film of dental plaque found on teeth. These reactions are responsible for painfully inflammed gum tissues and the wasting of bone that culminates in the loss of sound teeth in adults.

Significant strides were made in the study of herpes simplex virus through the establishment of an animal model system. This system provides an unparalleled opportunity to study the factors responsible for reactivation of herpes, viral reservoirs, and the effectiveness of immunization and drug therapy in preventing and treating herpetic eruptions.

Advances were also made in continuing research on events in the growth and development of oral-facial tissues. Among them, the formative sequence of the secondary palate and how certain drugs cause cleft in animals have been clarified.

Objectives for 1977: Studies of microbial causes of dental caries (tooth decay) will seek needed information about the individual bacterial species involved, events that lead to their colonization of the tooth surface, and the biochemical and genetic qualities that enable them to survive in the mouth.

Increased emphasis will be placed on furthering understanding of the mechanisms of initiation and progression of certain inflammatory oral disorders, notably periodontal disease. More extensive efforts will be made to document microbial and immunological mechanisms in periodontal disease and to develop measures to counter the destructive processes.

Substantive research continues to be directed to oral and facial pain. Laboratory and clinical studies will be undertaken to define and clarify pain mechanisms, develop reliable methods of measuring the acute and chronic oral-facial pain in humans, and determine effective means of controlling pain. Another area of emphasis is the physiological and behavioral effects of new short-acting sedatives used for controlling anxiety and apprehension in ambulatory dental patients.

National Institutes of Health

National Institute of Dental Research

Program Purpose and Accomplishments

Activity: Program Management. (Public Health Service Act, Title IV, Part C)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
30	$1,982,000	Indefinite	30	$2,101,000

Purpose: This activity provides the overall scientific and administrative management of the Institutes grant and contract programs.

Explanation: This office is responsible for providing leadership in the field of dental research managing research grant, fellowship and training programs sponsored by the Institute and developing and implementing contract supported research programs.

Accomplishments of 1976: The staff supported by this activity continues to provide scientific and administrative management of the Institute's research grant and contract activities. In 1976 an estimated 496 grants and fellowships and 63 research contracts will be funded.

Objectives for 1977: Program management will continue to provide for the overall admininstration of the grant and contract programs.

Transition Quarter Analysis

	Budget Authority by Activity			
	1976 Estimate		Transition Quarter	
	Pos.	Amount	Pos.	Amount
Caries	39	$9,717,000	34	$1,788,000
Periodontal Diseases		6,472,000		600,000
Restorative Materials		3,060,000		438,000
Craniofacial Anomalies		7,397,000		1,402,000
Pain Control and Behavioral Studies		1,840,000		32,000
Soft Tissue, Stomatology, and Nutrition		3,225,000		497,000
Dental Research Institutes		7,200,000		---
Intramural Research and Direct Operations	212	10,534,000	205	2,333,000
Program Management	31	1,982,000	30	834,000
Total obligations	282	51,427,000	269	7,924,000

Funds needed for the interim period are based approximately on monies required as if this period were another quarter in the budget cycle.

THURSDAY, FEBRUARY 26, 1976.

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

WITNESSES

DR. DONALD B. TOWER, DIRECTOR
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. RONALD W. LAMONT-HAVERS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ELDON L. EAGLES, DEPUTY DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
PAUL G. WAUGAMAN, 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
NORMAN MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. NATCHER. The committee will come to order.

We take up at this time the request for the National Institute of Neurological and Communicative Disorders and Stroke. We have before the committee Dr. Donald B. Tower, the Director of this Institute, along with Dr. Fredrickson, the Director of the National Institutes of Health.

Dr. Tower, we are delighted to have you and your associates with us. Before you start will you tell us who you have with you?

Dr. TOWER. Thank you, Mr. Chairman. On my right is Dr. Eldon Eagles, Deputy Director of NINCDS; on my left, Mr. Paul Waugaman, our new executive officer, and beyond him Mr. Sithens, our budget officer. I also have Dr. Fredrickson up at the table with us, as you indicated.

Mr. NATCHER. Dr. Tower, we are delighted to have you and these gentlemen, and you may proceed.

[Dr. Tower's biographical sketch follows:]

Name: 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 to 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.

Assistant Surgeon General, USPHS (Active), 1975 to present.
Medical Director, USPHS (Active), 1958–75.
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 Society for Neurochemistry.
International Brain Research Organization (Member, Central Committee).
Society for Neuroscience.

Special awards, citations, or publications:
Alpha Omega Alpha.
Sigma Xi.
Markle Scholar, 1951–53.
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 100 scientific papers and monographs.

Dr. TOWER. Mr. Chairman and members of the committee, it is again a privilege for me to be able to summarize for you accomplishments and current research programs of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

During the past year the NINCDS has completed its reorganization into its present programmatic structure. Directors have been appointed for each of the four extramural research programs: Dr. Wesley Bradley for communicative disorders; Dr. J. Kiffin Penry for neurological disorders; Dr. Murray Goldstein for stroke and central nervous system trauma; and Dr. Karl Frank for fundamental neurosciences. With the retirement of Mr. Eckart Wipf, Mr. Paul Waugaman has assumed the duties of NINCDS Executive Officer. Finally the appointment of Dr. George Murray to direct the NINCDS Office of Program Planning and Evaluation will provide for the first time the requisite staff backup for these program areas and the Institute generally.

COMMUNICATIVE DISORDERS

For the Communicative Disorders, the NINCDS is funding in fiscal year 1976 a total of 39 program projects, clinical research centers and other targeted research grants totaling $8.75 million, as well as more than 110 regular research grants, over 30 fellowships, and 13 contracts. Some of the major advances come from research projects on the effects

of noise and of ototoxic diuretic agents on the cochlea or inner ear; from newer techniques like fiber optics for visualizing disorders of the vocal cords in the larynx (or voice box); from studies on problems of language and speech acquisition; and from the use of a new technique called brain stem audiometry (an evoked potential technique) to test responses of infants and comatose patients to sound stimuli.

Special mention should be made of progress in implementing the recommendations from the workshops on the auditory or cochlear implants. Development of appropriate hardware (electrodes and stimulators) is underway. Ready for testing is the prototype of a new stimulator which requires no wires through the skin. It is called a transdermal stimulator which transfers the power or energy to an implant by radio frequency coupling, while the auditory or sound signal is fed to the implant by ultrasonic coupling. The two kinds of input are completely independent and flexibly controlled. Such a stimulator is likely to have much wider application for neural prostheses as well. By later this spring the careful evaluation of the dozen patients who have already received auditory implants will be completed and a detailed report will follow. As a result better planning for future work in this field will be possible.

NEUROLOGICAL DISORDERS

In the Neurological Disorders a total of 67 clinical research centers, program projects, and other targeted research grants are now being funded by the NINCDS at a level of $13.5 million, as well as some 700 regular research grants, some 170 fellowships, and 30 contracts.

In epilepsy, another new anticonvulsant drug, clonazapam (Clonapin), has been introduced into clinical practice, and dipropylacetate (Valproate) is due to come on the market during 1976 or early 1977. To develop more drugs, the NINCDS has initiated a screening program, enlisting the cooperation of pharmaceutical companies to supply potentially promising drugs for evaluation by a university laboratory for anticonvulsant efficacy and potency. As in the past the NINCDS will closely monitor, through its outside advisory committees and its staff, the progress in this program. During fiscal year 1976 the comprehensive epilepsy program got underway with awards totaling $2.3 million to three centers in Oregon (Good Samaritan Hospital); Minnesota, University of Minnesota and Mayo Clinic jointly; and Virginia, University of Virginia. We intend to fund one or two more comprehensive programs during fiscal year 1976.

In other neurological disorders some of the highlights are the following. In Parkinson's disease a new class of drugs called dopamine agonists, because they mimic the action of the natural nerve-impulse transmitter, is being evaluated. In neuromuscular disorders like polymyositis where there is significant muscle damage, the telltale influx of calcium into the damaged areas can now be quantified clinically by scanning patients after injection of radioactive technetium diphosphonate. The cause of the weakness in myasthenia gravis has now been shown to have an immunological basis resulting from a circulating immunoglobulin which prevents normal muscle stimulation—by the nerve-to-muscle transmitter—by blocking its access to the muscle receptor. The efficacy of prednisone therapy now becomes understand-

able because the drug acts as a suppressor of immune responses. As a result of the international workshop on diabetic neuropathy organized last summer by the National Commission on Diabetes and the NINCDS, we are planning to implement the recommendations as outlined in the Commission report recently submitted to the Congress.

Much of the data from the multiple sclerosis—MS—survey in the Shetland and Orkney Islands is now in hand and being evaluated. The study includes an examination of blood samples from MS patients and matched controls for profiles of the histocompatibility antigens, which are inherited in specific patterns, some being disease specific. One aim of the survey is to ascertain whether certain of these antigens are unique markers of diagnostic or screening significance for MS. In the area of slow and latent viruses, an NINCDS investigator has demonstrated that infections with measles virus suppress the T-lymphocyte immune response and hence antibody formation—observations relevant to MS and to SSPE. Another NINCDS scientist and several grantees are studying defective virus particles which can stimulate antibody production but abort infection of cells with intact virus, such as influenza, measles, or rabies.

The NINCDS perinatal research project will shortly be completed and key staff members are already being shifted to the developmental neurology branch within the neurological disorders program. One of their first activities was the organization of a workshop on the neurobiological basis of autism, which is being held today and tomorrow, February 26 and 27, 1976, at the NIH, with a distinguished international group of invited participants.

STROKE

For stroke and central nervous system trauma, the NINCDS is currently funding 70 program projects, clinical research centers, and other targeted research grants totaling over $15 million, as well as 60 regular research grants, 10 fellowships, and 13 contracts.

Stroke remains the largest single problem confronting the NINCDS both in terms of the extent of the public health problem and in terms of the nature of the stroke problem itself. Increasing attention is being focused on the transient ischemic attack—TIA—as one of the few warning signs that may precede a stroke. The TIA represents a temporary slowing or interruption of blood flow in a cerebral artery manifested by a transient interference with vision, speech, muscle power, or sensation. Such attacks last a few minutes to a few hours and characteristically leave no residual signs or symptoms. One study indicates that 80 percent of stroke patients have had one or more TIA's, and another recent study estimates that approximately 50 percent of patients experiencing a TIA will progress subsequently to a full-blown stroke. There is a growing consensus among stroke experts that a TIA should be treated as an emergency with prophylactic anticoagulant therapy and that multiple TIA attacks are indications for surgical intervention. In addition TIA's may also be predictors of subsequent atherosclerotic heart disease. Among the black population the incidence of TIA's is much less than among the white population in the United States. We need much more information about the importance and significance of TIA's in the stroke context. With the recent validation

by investigators at Duke University of a questionnaire for identifying IA suspects, NINCDS will initiate the planning and implementation of a prospective study in a large enough community population group to provide some answers to these and other questions.

With better acute management and surgical technology, the mortality in the United States from the most dangerous form of stroke, hemorrhagic stroke, has decreased by 20 percent. This decrease is associated with a significant shift in patient management from acute surgical intervention to medical therapy for the initial 10-day period followed by elective surgery to prevent bleeding.

By far the largest group of stroke patients—70 percent—sustain cerebral infarction or thrombotic stroke from a plug or clot in a cerebral vessel. For this group the NINCDS is proposing a pilot program of demonstration and evaluation of the transfer of "bench" results from a good clinical research team to the community. Implicit in the program would be the development of prognosticators from the acute stroke stage for appropriate rehabilitation measures in the subsequent management of patients.

For both stroke and central nervous system—CNS—trauma, a major factor in survival and recovery is the problem of the ischemic neuron—the nerve cell deprived of adequate blood supply, oxygen, and other essential nutrients so that it ceases to function and eventually dies. Because of the similarities in basic pathological mechanisms between head and spinal cord injuries, combination of some or all of the current NINCDS clinical research units into CNS trauma units is under consideration, as well as collaboration with the emergency medical services research program proposed by the National Center for Health Services Research of HRA.

The publication in September 1975 of the proceedings of the four workshops on central regeneration in the nervous system, sponsored by a subcommittee of the NANCDS Advisory Council, is expected to reinforce the generation of new projects in this area which is already occurring from workshop participants themselves. There are difficult problems here, but interest is aroused, and we anticipate significant research progress.

FUNDAMENTAL NEUROSCIENCES

For the fundamental neurosciences program, representing those projects in the basic research area not readily identifiable with one of the other three NINCDS extramural program areas, the Institute is supporting over 150 research grants, 9 fellowships and 13 contracts during fiscal year 1976.

From the diversity of productive studies let me mention a few examples: the isolation of pure nerve-to-muscle transmitter receptors from muscle by use of a specific binding agent, alpha-bungarotoxin, obtained from the venom of a Taiwanese snake; the tracing of nerve pathways within the spinal cord or the brain by horseradish peroxidase, an enzyme protein visible by suitable staining techniques under the electron microscope and with the convenient property of being taken up by nerve endings peripherally and transported inside the nerve fiber or axon up into the nerve cell body from which the axon originates; the discovery that opiate or narcotic receptor nerve cells in the brain release pentapeptides—compounds composed of 5 amino

acids—which mimic the effects of opiate drugs; and a growing number of studies on "plasticity" of the nervous system—the ability of the brain to adapt, to learn, and even to generate or regenerate new circuits or interconnections.

The neural prosthesis program of the NINCDS is a responsibility of the fundamental neurosciences program. A major advance in this area is the sophistication of a hand prosthesis for the quadriplegic patient to provide fine motor control, including pressure and slippage detectors, by use of improved implanted stimulators and feedback control.

INTRAMURAL RESEARCH

A number of examples of research from our laboratories at Bethesda have already been cited. The three new laboratories of neurootolaryngology, neuroimmunology and neuropharmacology mentioned last year are now staffed and fully operational. Among major intramural contributions are: those involving brain scans or computerized axial tomography [CAT] scans now operational at the NIH Clinical Center with a daily neurological patient load of 8–12 drawn from many Federal facilities; studies on a tumor angiogenesis or blood vessel forming factor whose titer is highest in malignant gliomas of the brain; continuing effectiveness of enzyme replacement therapy in Gaucher's disease; elucidation of structural similarities among choleratoxin, pituitary hormones and a major cell membrane constituent: G_{D1b} ganglioside, thus permitting an understanding of the mechanism of action of uptake of cholera toxin into cells and the potential for treating the eye complications of thyrotoxicosis.

Let me say parentheticaly, Mr. Chairman, this is an example of how the findings of one institute can extend over into the problems of other institutes, and the investigator who made these discoveries is cooperating with the investigators in two other institutes to exploit this observation.

Finally, experimental dissection of the mechanism by which neurotransmitter agents are released in studies that utilize the technique of freeze-fracture electron microscopy to permit us for the first time to understand the mechanism of action of botulinum toxin—botulism; and the demonstration that the specific myelin glycoprotein is on the surface of the myelin or fatty sheath surrounding nerves and hence may act as a receptor site for viruses or toxins in such demyelinating disorders as multiple sclerosis.

The informational activities of the NINCDS continue to be very active. At the NIH our institute has the only facility for producing audio and video tapes on experimental and clinical research subjects. This comprises a modest one room studio and tape-editing unit operated part time by one of the staff members of our Office of Scientific and Health Reports. The 38 video tape lectures on neuromuscular disorders, multiple sclerosis and other subjects are available on a free loan or purchase basis. They have proved exceptionally popular and are in constant demand.

The number of subjects is being continually expanded. A variety of other media and coverages are utilized. For example in the area of stroke there are reports from the Joint Stroke Facilities Committee, periodic research surveys, scientific abstracts published in the journal

"Stroke," an annual stroke bibliography, publication of the biennial transactions of the Princeton Stroke Conference, an article on stroke in the "Pharmacy Times"—reaching 80,000 pharmacists—and pamphlets for distribution to lay audiences. Such activities are duplicated in full or in part for most of the other major areas of concern to the NINCDS, including a number of special monographs issued during the past year like the 3-volume 25th anniversary work "The Nervous System", published in December 1975, copies of which have been furnished to this subcommittee.

In conclusion, Mr. Chairman, the budget request for the National Institute of Neurological and Communicative Disorders and Stroke for 1977 is $146,532,000. I shall be pleased to answer any questions and supply additional information as desired for the record. Thank you.

Mr. NATCHER. Thank you, Dr. Tower.

Now, Doctor, your budget request for 1977 is approximately $1,800,000 over the 1976 obligational level.

Dr. TOWER. Yes, sir.

COMMUNICATIVE DISORDERS

Mr. NATCHER. However, you are reflecting decreases in the communicative disorders program and training grants. Why were these reductions necessary, Doctor?

Dr. TOWER. Mr. Chairman, if I may take the two items separately, the reduction in the communicative disorders program and in fact in some of the other programs reflects primarily a decrease in the commitment base, that is, the grants that have been in force over the last few years which are terminating in the coming fiscal year.

So that there is a very significant reduction in the commitment base in some of the program areas.

TRAINING GRANTS

In addition, and another major factor, is the reduction in the so-called old training grants programs which will be totally phased out during the present fiscal year. There will be none of these in our training programs next year. This represents a reduction of something of the order of close to $4 million. That is spread in the way in which we have developed our budget for this year among the four program areas so that each reflects part of the reduction that you are referring to.

This phaseout of the training grant programs was one which was decided upon by the Department several years ago. Substituted for that is the new national research service award fellowship program which we are presently embarked upon. If the Congress votes the authorization for its renewal this year, we shall expect to continue and increase that particular fellowship program next year.

Mr. NATCHER. What would result programatically as a result of this reduction for the communicative disorders program? What will the impact be?

Dr. TOWER. Mr. Natcher, I think that the impact will be relatively small in terms of the research grants because most of that reduction

will be in the training area. As a matter of fact, a great deal of the reduction that has occurred in the noncompeting grants will be offset by an increased amount of money for the new and competing grants for next year.

If I may give you very quickly the net differences, the total net reduction is approximately $989,000, with $867,000 representing a reduction in the phase out of the training programs. So that we are talking about only a little over a hundred thousand dollars net reduction in the grant area, and I think you will find that in fact we have compensated for most of the reduction that is shown in the total in the new and competing grants and in additional centers.

I believe, sir, that we have a viable program there except in the training area, and I must confess, sir, that we have had some difficulty in encouraging applications for training in that area. We have tried to beat the bushes, impress upon the people in the communicative disorders field that we think they need more people in training because they have a great many problems to solve, and we have not been as successful as we would like. We are going to step up that program. We think it is extremely important.

TRAINING COMMITMENTS

Mr. NATCHER. The budget proposes to eliminate the training grant program. Will the individuals currently being trained under these grants complete their training prior to fiscal year 1977 or will they simply be left in the lurch?

Dr. TOWER. Sir, any commitments that have been made under the old program will be totally honored. It turns out from the way in which the trainees were brought into the program that essentially all of them will be finished except for a few of the Weinberger Fellowships which will spill over into the next fiscal year.

If my memory serves me correctly, it is only about $60,000 that will be in that particular area. All of the rest of the training money indicated for fiscal year 1977 will be in the new type fellowships under the national research service awards.

DIABETES

Mr. NATCHER. As you recall, Doctor, the committee in this report of the 1976 appropriation bill directed your institution to use a portion of the increased funds to expand your research efforts on diabetes.

Dr. TOWER. Yes, sir.

Mr. NATCHER. How much of the increase did you use for diabetes research, and what are your plans in 1977 for such diabetes disorders as diabetes nerve disease? This is a subject, Doctor, that we discussed yesterday and the day before. It is all important to the people in this country. What are you doing?

Dr. TOWER. We are extremely concerned about this ourselves. As you indicated, this is a major problem for diabetics. It is said that all diabetics experience some demonstrable involvement of their peripheral nerves, especially in the legs, that at least a quarter of these are symptomatic and that half of that latter group are partially or totally disabled. We estimate this involves something over a half million patients who are in the disabled category, with the pain, loss of sen-

sation, increased chances for injury and ulceration to the lower limbs.

The Diabetes Commission and our Institute worked together very carefully on this. We held a workshop last August with experts brought in from around the world. There are unfortunately very few of them. It is unfortunate there have been so few people who have become interested in this problem, and that of course is one of our aims and one of the recommendations of the Commission, that we initiate a fellowship program which will increase the number of people expert and interested in this area.

So that one of the initiatives which we will begin during this fiscal year and increase during the next fiscal year deals with providing fellowships. We propose to fund several during the fiscal year and double the number next fiscal year.

We have allocated $40,000 this year and $80,000 next year for this purpose, and then continued increases over the subsequent 3 years for a total of a 5-year program, as recommended by the Commission.

In addition to that we propose to increase the basic research and clinical research effort in the area of diabetic neuropathy by adding approximately $141,000 this year and essentially doubling that next year for research in this area, also as recommended by the Commission.

In order to get this off the ground as rapidly as possible, we are proposing to use much of this research money to supplement the programs that we already have in nerve and muscle disorders with the specific direction to them to increase their efforts, particular in the area of diabetic neuropathy. One of the problems here is that we do not understand enough about neuropathies in general, and therefore we need some basic research to back up the specific area of diabetes. There is a question of whether the involvement of the nerves is a result of involvement of the blood vessels which nourish the nerves characterized by a narrowing of the caliber of the blood vessels because of arteriosclerosis that is associated with diabetes, or whether the effect on the nerve is a direct effect of the disorder of glucose metabolism, which is characteristic of diabetes. If we solve this problem we may be able to deal most effectively with the problem of diabetic neuropathy, so basic research must go hand in hand with the clinical research. We wanted to put this in the hands of the best experts we have to speed up the results as much as possible.

COCHLEAR IMPLANT

Mr. NATCHER. Doctor, reference is made in your material and in the statement that you have just given to our committee about a so-called cochlear implant which will restore hearing for millions of individuals with hearing loss. When do you expect this technique to receive wide application?

Dr. TOWER. Mr. Natcher, if I may slightly modify your statement. We are not sure that this will be as widely applicable as you may have been led to believe. We hope it may be. We don't think we have such information yet.

What we have done is to sponsor two workshops which were held in 1974 in which we brought together all the experts in this country, both basic and clinical. The second workshop, of which I have a summary pamphlet here and which I would be glad to leave with the com-

mittee, was held in San Francisco in October 1974, actually a little over a year ago, at which time a series of recommendations was developed across the board from the basic science information and the research that was needed right up to the evaluation of those patients who have already had the so-caled cochlear implant.

That later evaluation is going on right now at the University of Pittsburgh, and it will involve 12 patients at least out of a total of approximately 20 we know who have had the implant in this country.

Through the cooperation of the physicians who carried out the operation and the patients themselves, this will provide us with an idea of what actually has been provided in the way of benefits to these patients, what the problems are and the way in which future patients ought to be screened ahead of time for those who would gain the most benefit or the least benefit from the procedure. At the same time a great deal of both grant and contract research is now going on to develop the necessary hardware and the information to know the best way to proceed.

The problem, sir, is basically this. If you destroy the inner ear, the cochlea, where the sound coming to us is converted into the electrical or nerve energy, the only interface that you have left between the outside and the brain is the nerve, which is essentially a raw ending. If I may use a rather oversimplified analogy, it is like cutting a cable which is coming from a complicated powerplant and going out to serve the community, and all you have is the end of the cable left.

If it is a telephone cable, it is quite a difficult job even if you were to succeed in making the right reconnection to that. If in addition some of the wires in the cable have been destroyed in the process, as seems likely in some cases, you may not be able to restore completely useful application of sound.

One of the things that has to be borne in mind is a distinction here between just sound, a buzz or some other kind of attention-getting device, and the ability to understand speech. We do not at the present time feel we are in a position to say that we can at all restore the opportunity to understand speech. That is something which I think is for the future to decide.

So at best we are confronted with a situation now in which we may have a better sound-alerting device, and what the future holds will depend upon the basic and applied research that we are engaged in supporting right now.

COST OF IMPLANT

Mr. NATCHER. Doctor, what about the cost; will the cost place this implant in a position where it is completely out of the reach of those who need it?

Dr. TOWER. Mr. Natcher, the cost will be considerable. There is no question about that.

Mr. NATCHER. When you say considerable, do you have any idea, Doctor?

Dr. TOWER. I don't really have an actual idea because it will depend on the number of patients for whom the implant would be indicated, and therefore what kind of mass production or tailored production would be required, but I would guess that the cost is going to be of the order of a good many hundreds of dollars. It will certainly be more expensive than even the better hearing aids that are available now, and

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it will require a considerable amount of additional cost in terms of retraining the patients, in terms of speech, and the responses to the sounds that they perceive, so that in the beginning this will be a very costly procedure.

Now, if it works well enough on a lot of patients, obviously the costs will come down, but I think it is too early to say really more than that. I wouldn't like to get too far out on a limb there until we see exactly what we are able to do with this problem. However, we are able to miniaturize the devices and that sort of thing.

OTITIS MEDIA

Mr. NATCHER. What is the status of your research on otitis media? What is this middle ear derangement?

Dr. TOWER. Yes, sir. We have two major kinds of infections there. One is the acute one that you and I were familiar with as youngsters, one that frequently led to mastoiditis. That has pretty much gone out of the picture because we have an antibiotic and surgical therapy to deal with that. We don't have as much problem with that provided it is picked up early enough by the family physician.

However, there is a condition known as serous or secretory otitis media, which is a chronic infection of the middle ear, particularly in children, which is a very troublesome problem at best, and at worst may impair hearing in children in school years.

There is a considerable difference of opinion in the community of otolaryngology—the ear, nose, throat people—about whether this should be treated in a vigorous fashion or whether it will just clear up by itself. We have had several workshops; we have just completed one; and the information is emerging to try to provide us with the best consensus as to where we should be going with this problem and what research is needed.

I believe by next year we shall be able to answer this question a little more successfully for you than we can right now. The difficulty right now is a very considerable difference of opinion in the otolaryngological community about how to deal with this question. It is a clinical problem and, as you know, clinical research particularly in areas like this is especially difficult. We don't have a good animal model and, therefore, we have to deal with the constraints of the human organism, and this has impeded the progress somewhat.

LANGUAGE AND SPEECH

Mr. NATCHER. I notice in your budget justification that you are directing some of your research toward developing methods for screening preschool children in language and speech problems. Specifically what are you doing in this area at this time?

Dr. TOWER. We have several very active programs going on to deal with a number of different facets. Those children that come with impaired hearing, from whatever cause, fall into one category in which we need to have some idea about how well they benefit from early fitting of hearing aids, what problems they have in noisy classrooms and other environments in trying to acquire speech, and understand what is going on.

NOISE

In addition to that, we have just had a study completed for us on the effects of noise on young children. This is an area which has been very much neglected, and about which there is really not as much information as we would like but there are indications of some very important problems that need to be investigated there.

These and other similar studies we have developed over the last couple of years in order to get an idea of the dimensions of the problem and to allow us to design the best approaches to deal with this.

I want to emphasize that this is an exceptionally important area. Children during the preschool and early school years must have optimum opportunities for communication, both incoming and outgoing, that is, both the hearing and the speech aspects.

Things that interfere, we feel on the basis of the knowledge we have available to us at the present time, are extremely serious in holding back the ability of these children to acquire speech and language expertise at the most critical times in their development. Hence this is an area of research which we feel is extremely important and needs a great deal of effort.

There are not as many people available to do this research as we would like, and therefore I come back to my earlier statement that we must train more people in this area. We need more expertise to attack this problem.

COMPREHENSIVE EPILEPSY CENTERS

Mr. NATCHER. How many comprehensive epilepsy research centers are you currently funding and what are your plans for 1977?

Dr. TOWER. We are funding at the present time three—one in Oregon, one in Minnesota, and one in Virginia. We expect to be able to fund at least one more and perhaps two more during this year. I think we will not fund any additional ones in 1977 because I think now is the time for the shakedown to see how these 4 or 5 will function, to get an idea of what problems they may encounter that we hadn't anticipated, how well they are able to interface their role in the clinical research area with the delivery of the community services that forms a part of this comprehensive program.

So 1977 will be a year in which we will be assessing how we are doing.

ANTICONVULSANT DRUGS

Mr. NATCHER. You stated that another anticonvulsant drug, clonazapam, has been introduced into clinical practice. Does this mean, doctor, that it is readily available to all physicians and their epileptic patients at this time?

Dr. TOWER. Yes, sir, it is on the market. It is available to all physicians. This is another example of how we have achieved a very effective collaboration amongst the clinical community, the pharmaceutical industry, the FDA and our Institutes in getting this drug to the market in a reasonably short time.

Mr. NATCHER. Specifically, doctor, what does a new drug like this one mean to someone with epilepsy?

Dr. TOWER. Mr. Natcher, let me put it this way. From 1960 until 1974, we had not one single new drug for epilepsy introduced in this country. In 1974 we brought in the first new drug carbamazepine or Tegretol, which has proved especially helpful in certain types of seizures that we call complex partial seizures that affect particularly the brain area right over the ear.

We have now brought in clonazapam which is particularly useful for the generalized seizures, especially what we used to call petit mal, which are especially common in childhood and can be devastating for the child in school. If the child has too many seizures, he or she misses out on the teaching activities and falls behind.

We have also learned if we do not control these particular seizures during early childhood there may actually be damage to nerve cells which cannot be rectified later on, and we may actually have subnormal intelligence develop in children who have too many of these seizures because of lack of effective treatment. So this is an exceptionally important development particularly in the childhood period. We are delighted to have this drug available because it is one of the more effective ones that has been introduced over the whole history of antiepileptic therapy; it is going to zero in on this area which is so important in the growing child.

Mr. NATCHER. Doctor, is this another expensive drug and one that is beyond the means of most people?

Dr. TOWER. It is expensive. I can't tell you offhand how much it is. I can supply that for the record since I didn't bring that information with me.

[The information follows:]

COST OF NEW ANTIEPILEPTIC DRUGS

The Institute's role in the development of new antiepileptic drugs has been to support controlled clinical evaluations which the pharmaceutical industry has had great difficulty in otherwise obtaining. The Institutes have research contracts for investigation of new drugs for the treatment of generalized tonic clonic seizures—grand mal—absence seizures—petit mal—and complex partial seizures—temporal lobe or psychomotor seizures. The epilepsy branch sponsored three controlled clinical trials of carbamazepine—Tegretol—which subsequently was marketed in August 1974. The patent for the drug was issued in August 1960, and will expire in August 1977: Tus the patent protection for Tegretol is for 3 years. An informal telephone survey of pharmacies in the Metropolitan Washington, D.C., area, indicated the cost for a day's supply of Tegretol to be from 41 cents to 50 cents. This cost is significant, and approximates the cost for patients with other chronic conditions, such as hypertension. Clonazepam—Clonopin—was investigated by the Institutes in two controlled studies. The drug was marketed in August 1975. The cost to the patient is approximately 20 cents to 23 cents for a day's supply. For comparison, two older established drugs would cost the patient as follows: Dilatin from 6 cents to 9 cents for a day's supply, and Mysoline from 24 cents to 26 cents. As the newer drugs are reserved for patients who fail to respond adequately to earlier drugs, the physician would prescribe the newer drugs only upon demonstrated need.

Mr. NATCHER. How about the middle-income class family now; can they afford this drug?

Dr. TOWER. Yes, sir, they can afford it but it places a strain on the budget, and certainly people below middle income, in the lesser income brackets, will have a great deal of difficulty. This is a very serious problem.

I may say this is one of the kinds of problems that our comprehensive epilepsy programs are designed to deal with, because we will get a great deal more experience and knowledge than we have now about just what the impact of this problem is at the community level.

AUTISTIC CHILDREN

Mr. NATCHER. Doctor, each year we talk with you about autistic children. Have you learned any more about the cause of autism?

Dr. TOWER. Mr. Natcher, if I weren't down here right now I would be at the meeting that we are having out at NIH in which we have an international group of experts together to talk about just exactly what the problem is with autistic children. We have a conference going on right now today and tomorrow which will cover the whole subject, definition, biochemistry, physiology, language problems, psychological problems.

Tomorrow morning, when I will certainly be there, we will formulate a set of recommendations for both the community and for the Institute as to where we should go in this very devastating disorder.

Mr. NATCHER. Doctor, if it is not too much trouble to you, could you prepare for us a short statement of what will take place out there today and tomorrow, and submit it for our staff's use?

Dr. TOWER. We will be most happy to do that.

Mr. NATCHER. Let's insert it in the record at this point.

[The information follows:]

PRELIMINARY SUMMARY

WORKSHOP ON THE NEUROBIOLOGICAL BASIS OF AUTISM

A workshop on the neurobiological basis of autism was held by the National Institute of Neurological and Communicative Disorders and Stroke, on February 26 and 27, 1976, on the National Institutes of Health campus, Bethesda, Md. The goals of the workshop were: (1) To formulate a working definition of autism to serve as a common basis for neurobiological research; (2) to provide assessment of the current status of neurobiological research on autism; and (3) to identify promising research areas and provide recommendations for research activities to advance scientific knowledge of the neurobiological basis of autism. The workshop was attended by 55 scientists from academic institutions and government. They included neurologists, pediatricians, psychologists, neurophysiologists, biochemists, speech, language and hearing specialists, and psychiatrists. Government agencies represented were the Bureau of Education for the Handicapped, the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the Division of Developmental Disabilities, Rehabilitation Services Administration. The presentations and discussions centered around the following topics: definition, neuropsychology, language, neurophysiology—vestibular and evoked potential research—and neurochemistry.

DEFINITION

The definition of childhood autism is best made in terms of four essential criteria: (1) onset before the age of 30 months; (2) impaired social development with a number of special characteristics out of keeping with the child's intellectual level; (3) delayed and deviant language development which also has specific features out of keeping with the child's intellectual level; and (4) insistence on sameness as shown by sterotyped play patterns, abnormal preoccupations or resistance to change. The syndrome defined in this way has been shown to be valid and meaningful in that it differs markedly from other clinical syndromes. Autistic children must also be described in terms of mental age and the presence or absence of neurological or other medical disorders. Investigations which fail

to equate groups of study and control children for mental age are almost uninterpretable. While it is suggested that a 30-month cutoff be made for the onset of autism, study of children with known biological insults at later ages who develop the autistic syndrome may be of research value in delineation of mechanisms of autism. Work is needed to define and describe precisely the essential components of autism. Knowledge is lacking whether autism in children of normal intelligence is the same as autism in those who are mentally retarded. With severe mental retardation the features of autism become more muddled. Greater research focus on autistic children without mental retardation or other neurological disorders would be especially profitable.

NEUROPSYCHOLOGY

Diagnostic tools must be sharpened. Parental questionnaires are useful for screening but need to be validated before they are used to establish clinical diagnoses. Longitudinal studies are needed to follow groups of infants who may be at high risk for autism, and to follow autistic children for fluctuations in behavior over time. Investigations of preconception history and of the events of pregnancy are needed in attempts to establish etiology. There is a need for independent research to evaluate and categorize autistic children. This would include the development of multidimensional descriptive scales for rating children by parents, educators, psychologists, et cetera. Since the determination of mental age in autistic children is essential but presents many problems, special procedures and methodologies need development and standardization. Correlations between autistic behavior patterns and neuropathology are needed. In instances where autistic behavior was identified and neuropathological materials examined, no consistent pathology was found. Recent findings by EMI or brain scanner of unilateral changes in size of the temporal horn in autistic children, and recent reports regarding herpes simplex encephalitis resulting in transitory autistic symptoms during the recovery phase, may help in the understanding of some cases of autism.

LANGUAGE

Research in language remediation and in language behavior of autistic children should be pursued. Recommendations include the development of language remediation procedures for the speaking group of autistic children, alternatives to direct imitation of the adult as a mode of presentation for language, guidelines to help a clinician decide which program, including sign language, is most appropriate for the autistic child, comparative studies of remedial techniques, and a description of the relationship between language growth measured several ways and improved functional use of language. In the area of language behavior more descriptions are needed comparing language development of children who are developing normally and those who are not. Better understanding of interaction between language skills and communication intent by an analysis of spontaneous language samples collected in different social situations might be helpful. Within social context and development level, qualitative descriptions of "echolalia" and "pronominal reversals," frequntly mentioned in literature concerning autistic children, are needed. The history of language development and the current level of language function in each autistic child should be precisely documented.

NEUROPHYSIOLOGY

Preliminary work suggests that vestibular—balance—and other sensory mechanisms may be impaired in autistic children. These studies indicate the need for more extensive work on the vestibular adaptation mechanism, habituation, variation in the types of vestibular response, the effect of vestibular stimulation on other modalities of sensory input, and the interaction of visual and vestibular systems in an attempt to clarify a possible role of vestibular mechanisms in autism.

There are reports of sensory-induced EEG—brain wave—changes in autism, but conclusions from these reports cannot be drawn because the studies are few and most of them have not been replicated. Based on research thus far, evoked potentials do not show the degree of abnormality which might be expected if this measure indirectly reflects the severe disorders of autism. Recording evoked potentials in the brainstem and then at successively higher levels in the sensory pathways may show that autistic patients have abnormalities in the transmission of sensory

information. The application of electrophysiology to the study of human language processes is also potentially fruitful. EEG and sensory-evoked responses may provide measures which can be related to functional specializations of the cerebral hemispheres.

NEUROCHEMISTRY

Findings reported on the biogenic amines in autism are conflicting. Chemical findings must be related to behavioral and other characteristics. Serial measurements are needed to correlate specific behavior of autistic childrn with biochemical concomitants. Animal models can be developed for single signs of autism, but as language defects are central to the autistic syndrome, an animal model has intrinsic limitations. Hypotheses of relationships between specific biochemical agents and autism may have heuristic value, and may suggest further experimentation leading to more precise understanding of the disorder.

PUBLICATION

The proceedings will be published and will contain the presentations, formal and informal discussions, and recommendations.

Mr. NATCHER. What research will you support in this field now as far as fiscal year 1977 is concerned?

Dr. TOWER. It will depend on the recommendations that come forward, sir. Certainly there will be some basic research which I think we can pick up rather quickly. What we would propose to do in this case on the basis of recommendations is to issue what we call a RFA, a request for application for grants in the basic science areas which are important. There are recent indications that some of the transmitter substances that mediate the transmission of impulses from one nerve cell to another may be defective in this case, and we have a whole body of experts out in the field that are working in these areas, that once they get the word as to where particularly to look, I think we may be able to facilitate basic research in that area.

IDENTIFICATION OF AUTISM

In addition, I would expect some recommendations to come out dealing with the identification of the children and precisely what criteria to use in order to define who is or who is not an autistic child. This is in something of disarray in the field and is one of the purposes of having this particular workshop, to find out precisely what criteria ought to be used and how we can set up not only the identification of the children but how we can then monitor them to see whether any of the therapies that we hope will be developed as a result of our research are influencing these children.

STROKE CENTERS

Mr. NATCHER. In your budget justification you state that you plan to initiate a program of comprehensive stroke centers. How many of these centers will you support, and specifically what will these centers do, Doctor?

Dr. TOWER. We expect to start off with a pilot program, sir, in which we will probably support two centers to begin with. What we are concerned with here is the period of 3 to 6 months following the stroke in which patients will improve to some extent in most cases, and in which various kinds of rehabilitation measures will be most important.

At the acute phase of the stroke, which is where we have been most

concerned in the centers that we support so far, from how the patients are handled during that time and what types of therapy they are given and the precise nature of the stroke which they have sustained, what we need to know is whether we can predict what kinds of rehabilitation and other types of chronic therapy in the poststroke period are most important, and which patients will do well and not do well.

We don't have such information now.

In addition, this is the kind of problem where you need to interface between a very sophisticated clinical research team in a university center and the whole community.

This is a problem which I think we need to address ourselves to much more, so that we are going to engage in a pilot program which will be really a demonstration and evaluation type of approach for this aspect of the stroke problem. But we need to move a little cautiously until we find out how best to go and where the limited number of dollars we have would be best invested.

PUBLIC INFORMATION

Mr. NATCHER. How do you intend to inform the average family practitioner about the latest stroke management procedures or stroke rehabilitation techniques?

Dr. TOWER. As part of our pilot program I just spoke about, we plan to step up the abilities through these centers and their movement out into the community with the followup to bring in the physicians and other hospitals and the community in general to learn a great deal more about stroke. We have discussed some of the ways in which we think this can be done.

In addition to that, as I indicated in my opening statement, we will have a variety of programs in our information area to provide information about stroke, and we propose to step this up. I think the video-tape facility that we have will lend itself particularly to this. We hope to develop some tapes which will be particularly helpful to the general practitioner, and to be able to distribute them widely.

I think the most effective way is to put the tapes into meetings at hospitals and medical societies, where they can be scheduled ahead of time at the most opportune time for the physician to be there and to see them. By making them into video tapes which we can lend, or if they want to buy them and have them permanently available they may do that too, but we lend them free, they can schedule them at a time when most of the physicians can be present and obtain the best coverage of this particular subject.

SPINAL CORD INJURY

Mr. NATCHER. On page 202 of your budget justification you state, "Preliminary data indicate that if the acutely injured spinal cord is treated immediately, and adequately, permanent damage may be minimized or prevented." Doctor, it would seem to me in order to achieve this level of care, you need a sophisticated emergency medical service and highly trained people. Are you working with the emergency medical service program of the Health Services Administration to achieve this level of care?

Dr. TOWER. We are working with them, sir, and we propose to work much more closely with them. The Health Services Administration has through its emergency medical research program proposed to do a good deal of research at the community level on this, and we wish to participate because we think this is the right way to go to deal with this particular problem.

In many areas where we have centers or major projects in the area of spinal cord injuries, we are already collaborating with them and with the rehabilitation centers that have been set up by the other agencies within HEW or by the Veterans' Administration.

This is clearly a much bigger problem than we are able to deal with our research dollars alone, but I think that the information we can develop over the next couple of years by the research into emergency medical services of this type will provide us with the means to amplify the impact of the information and the techniques we will develop.

COLLABORATIVE PERINATAL PROJECT

Mr. NATCHER. You state in your material that you have final data from your perinatal research project. Will you review for the committee some of the results of this project, Doctor?

Dr. TOWER. Yes, sir. We have a whole series of monographs coming out. Three of them have been published already. There will be another seven major ones later on, and there will then be a series of specialized monographs dealing with the analysis of the results of this project which has been going on over the last 15 or more years.

We now have the information on the preschool intelligence quotient, we have information coming out on febrile seizures in childhood, information on cerebral palsy. We are beginning to have a considerable amount of information in a great many other areas as these monographs develop.

The analysis of the data which involves close to 50,000 mothers and their offspring is a rather monumental task, but most of it will be completed by the end of this fiscal year; some will spill over to the next fiscal year. I don't know that all the monographs will be out by fiscal 1977 but we certainly hope so.

Most of the major work has been done now. It is mostly in the computer and being generated out in the types of programs that we have developed for analyzing the raw data.

But I think this respresents a body of data which certainly will be unique. I don't believe this type of study will ever be done again. It has been extraordinarily expensive and time consuming for all of us, but the nice thing about it is that the data itself and a good many of the samples will be available for future study. For example, we have frozen sera that we are storing out at Bethesda that we can go back to and ask questions about later on that we hadn't even thought about when we first started the study. This has already been done. I believe that we will gain manyfold in the long run from this study, far more than we expected when we first started out. I would be glad to supply you with the additional specific information if you would like to have it.

CHIROPRACTIC RESEARCH

Mr. NATCHER. Doctor, we hear from the osteopathic physicians and the chiropractic profession that more research is required in spinal

manipulative therapy. What research are you supporting in this area?

Dr. TOWER. We are not supporting as much as we would like to, Mr. Natcher, because we have not generated many proposals that have passed the study section peer review system. I believe that in the balance of this year and next year we are going to see a considerable upsurge in proposals that deal with spinal manipulative therapy. We have in-house now several proposals that are under review. We have a few ready to fund as soon as our present appropriation is apportioned to us, and I believe we will be able to cite to you a much better record by next year.

The problem particularly in the chiropractic community has been that they have not been really geared to the kinds of granting procedures that we have available, and it takes them a little while to learn. We have been sending some of our people to their meetings to clue them in as to how they can apply for grants, what kinds of research they ought to be dealing with, and urging them to get people trained in the research area. There is a very serious shortage of research people in the chiropractic community, so it is going to take them a little while to gear up. But we are supporting research in this area at a modest level at the present time. When we receive our apportionment, I think we will have about a quarter million dollars in grants that we can award. There are about 12 in the review process now. I don't know how many of those will survive through the funding stage but we expect some of them will.

INFORMATION PROGRAM

Mr. NATCHER. In your statement to the committee, Doctor, you referred to your active information program, and you are to be commended for giving this high priority. However, I don't understand why it is necessary for you to invest your limited money in a facility to produce audio and video tapes when the National Library of Medicine has a $3 million audiovisual center. What about that, Doctor?

Dr. TOWER. That is true, Mr. Natcher. I don't believe really, though, that there is an overlap. The National Library of Medicine has a very large program which deals in somewhat different matters than we do, and I believe we really have made a very modest investment. My rough guess is that we have put about $15,000 into the equipment and the time that has been involved. The return and the kinds of tapes we are able to produce is worth manyfold that amount.

We have the ability to move at the moment without going into a lot of redtape with another group to tape lectures of people who come to NIH and to go out to various meetings. For example, we are taping the results of the autism conference that is going on at NIH right now. We can just call our man in and take equipment up there and tape it. Only the cost of the tape is involved plus his time which we pay for anyway. So I believe that this is an exceptionally important capability to have in house.

It is also very important for our research program to be able to do this directly rather than having to go and deal through the National Library of Medicine. I don't consider the two mutually exclusive, and I believe that what we are able to do complements rather than overlaps what the National Library of Medicine is doing in its program.

X-RAY SCANNER

Mr. NATCHER. Doctor, I want to direct your attention for just a moment to the stroke and nervous system trauma program.

What results have been accomplished over the past year with the use of computerized axial tomography?

Dr. TOWER. This has been an exceptionally useful technique, sir. It is what we call a noninvasive technique for being able to examine the brain and now the spinal cord. By noninvasive I mean we don't have to inject anything into the patient or submit them to any operative procedures.

This is a very modest X-ray exposure, that allows us to obtain essentially a disection of the brain, and the parts of the spinal cord in a few minutes.

Mr. NATCHER. Doctor, is this an X-ray scanner hooked to a computer?

Dr. TOWER. Yes, sir, that is correct. What it does is to send X-rays through areas of the brain or the spinal cord, and determine differences in density. If you think about it as a black and white picture, those parts that are white, gray, and black are seen by the X-ray as differences of density and the differences come out in a numerical form which is fed into the computer.

The information in the computer is available for analysis in any form you want including generating a picture for you so you can actually see what the X-ray beams have seen. It is really an astonishing technique for us, because it allows us to see for the first time structure in the brain by this technique which before we could only see it on the post mortem examination.

COST OF SCANNER

Mr. NATCHER. Is this a real expensive system?

Dr. TOWER. Yes, sir; the instruments cost in the neighborhood of $400,000 to $500,000.

Mr. NATCHER. How are you going to bring it down so we can have that at Bowling Green, Ky., Doctor?

Dr. TOWER. There are two ways to deal with that, Mr. Natcher. One is to increase the number being produced so the price comes down, but I am not sure that is going to occur the way the economy is going these days.

The other is to recover the cost, as most places do, by charges to the patients. You may argue that increases the cost of medical care, and that is certainly true, but you can pay for the machine by relatively modest charges to the patients for the examination, and this is, in fact, what most places are doing.

At NIH we have two of these machines at the present time and we have another one on order.

These, of course, will be used for research purposes and we don't charge anybody for them out there. The Federal patients that come for the brain scans now come for free and we are drawing them from the VA and military hospitals and others around the Washington area. It's the only Federal facility in the area that has such a scanner at the moment.

This has been a revolutionary technique in dealing with such problems as stroke because you can get a much better idea of what the diagnosis is, then use the technique to monitor the course of the patient, make sure he is improving, and not getting into trouble. It adds immeasurably to our research knowledge of how best to handle these patients.

Mr. NATCHER. Thank you, Doctor.

Mr. Michel?

Mr. MICHEL. Thank you, Mr. Chairman.

DYSLEXIA

Dr. Tower, the television program, "60 Minutes" recently had a segment on dyslexia where children read everything backward. Are we doing anything in this area?

Dr. TOWER. Yes, we are. This is a responsibility of our Institute, although the Child Health Institute is also involved because this involves general problems of maturation and learning.

This is an area which deals with the broad subject of learning disabilities of which dyslexia is one of the major components.

It is a very curious phenomenon in which most people have concentrated on the reading or visual side, if you will, but it appears from some of the evidence that this may also involve the auditory system and the sound input, as well. I think really it is fair to characterize this as a problem in central processing, if you understand what I mean. The incoming signals have to be properly meshed, recognized, and then an appropriate output result from it.

The central processing for both visual and auditory and other types of sensory input is really at the heart of our basic research now, because we still don't understand precisely how the nervous system does this.

Mr. MICHEL. Isn't it possible, to have gone all through life and really not realize that one has had it?

Dr. TOWER. Yes, that is correct. You know there are some very famous people, including Vice President Rockefeller, who have this problem, and it is possible by certain special education techniques to overcome or at least minimize the problem, but it has to be recognized in the first place.

Mr. MICHEL. What are we doing to recognize this early in life?

Dr. TOWER. Well, this really is a problem for parents and particularly for the schools because it often doesn't become obvious until a child gets in the school system. This is really a problem in special education for which school systems need more help, and I believe it is our primary responsibility to get results of our research out to them. It is really a service area rather than research area in terms of recognizing kids, and many school systems have speech pathologists and audiologists available to them who are knowledgeable about this area. More school systems ought to have this type of expertise available.

AUTISM

Mr. MICHEL. Now, last year you told our committee you were going to conduct a workshop which would bring together people who have knowledge about the problem of autism.

Dr. TOWER. Yes, sir.

Mr. MICHEL. And I guess from your statement you have reached this point.

Dr. TOWER. It is going on right now, sir. It started this morning and they will finish tomorrow.

Mr. MICHEL. What do you expect this conference to accomplish?

Dr. TOWER. I think we will get a very good idea of what the current situation is with respect to this problem. We will have summarized for us, by the people we have brought together from both this country and abroad, where we stand on theories of what autism is, why it occurs, and how do we recognize patients, how do we evaluate them in terms of any potential therapy that is available, as to whether they are doing well or not doing well.

A series of recommendations will be developed tomorrow morning as a result of the scientific presentations which are going on today, and these will indicate to us what the best next steps are.

Mr. MICHEL. How many people are involved in this conference?

Dr. TOWER. We have close to 60 people out there invited but I don't know how many more in the audience, since it is an open meeting available to anyone who wants to come.

STROKE

Mr. MICHEL. Your statement indicates that mortality from strokes is down by 20 percent.

Dr. TOWER. That is for hemorrhagic strokes or just one type of stroke.

Mr. MICHEL. What about disabilities resulting from strokes?

Dr. TOWER. Well, this is a spectrum all the way from no-disability to almost total institutionalized care. The latest figures which we have, which you may understand are a few years behind because it takes a long time to collect and analyze such statistics through such agencies as the National Center for Health Statistics, where they must be age adjusted and all of that sort of thing before we can really deal with them, but the latest statistics indicate that about 10 percent of the stroke survivors are able to return completely to work, that about 15 percent at the other end require total institutional care, and the rest in the middle represent the spectrum between the two extremes.

I believe that we are going to be able to improve on these statistics, and that is one of the reasons for embarking on this pilot program, I was telling Mr. Natcher about a minute ago, of these two comprehensive stroke programs where we want to couple the acute phase with what happens to patients afterward. This has not been well done before and we feel that it is time to concentrate on this problem. I think we will be able to answer the questions much better in a couple of years when we have had a chance to see what the outcomes are.

Mr. MICHEL. Well, I have a more personal interest in your Institute this year over last year. My father last week—he turned 87 in October—he had a very slight stroke. There is no speech impediment or real physical incapacity, other than in sight, and in quick thought process.

He was an insatiable reader in his elderly years, and apparently part of the vision, right side, is blocked out. I was interested in reading your testimony with respect to transient ischemic attack; is that it?

Dr. TOWER. Yes.

Mr. MICHEL. Because as I perceive him now, he would like to read from right to left. When he came over to our house around Christmas time, everything was backward. He felt really like he was kind of in a new house, but he had been there for many years. Going back across town, several of the things appeared to be the same way.

Now, I notice in reading your testimony something to the effect that it could be one of those things that is initially detected in sight or in the eye.

Dr. TOWER. Very often this is the first symptom, but not necessarily. It depends on which particular vessel or which area of blood supply is involved. And usually it is on one side.

I must say, if he has gone to the age of 87 before having any problems, he has done much better than most people do. But that still doesn't solve the specific problem. He probably will experience some improvement, but it is very hard to tell at the present time how much.

A great deal of adjustment will be possible once he learns how to cope with the fact that part of his visual field is no longer functioning.

Mr. MICHEL. That is the big problem that comes with rehabilitation, because I think he loses interest. Well, I say you can't read, how about watching television more frequently? As a matter of fact, when it first happened the way my mother detected it, within 15 minutes he said I don't want to watch it anymore, and walked in the opposite direction to turn it off, and she quickly got him to the hospital. But he can't follow it that quickly anymore, like he used to, and I said how about the news stations where the news comes over 24 hours a day; is it possible then to get it refreshed enough that you still have that interest, because once the interest goes, his whole outlook would tend to decline.

Is there any kind of advice we could give a patient of that kind, to keep his interests alive?

Dr. TOWER. Yes, sir; there are a lot of things that could be done, and I would be glad to try and give this to you in a little fuller fashion than is possible right now.

I will be very happy to get this information to you. Does he live in your area?

Mr. MICHEL. Yes.

Dr. TOWER. There are a number of places out there we could suggest to you that will be helpful to consult with as well.

Mr. MICHEL. I appreciate that.

WORKSHOPS

How many workshops are you planning this year?

Dr. TOWER. I am not sure I can answer with a precise number right offhand.

We have a number of them planned in various areas; for example, one is planned for spinal cord injury research in May and another is planned shortly to deal with how drugs act in controlling epilepsy.

We have developed workshops on the basis of need rather than any specific number.

Mr. MICHEL. What does their average cost run, if you have a workshop of this kind?

Dr. TOWER. Well, workshops generally involve 15 to 30 people as

the active participants, and you can figure somewhere around $1,000 per participant for a couple of days' workshop. That includes the travel and their per diem and so on, so we are talking about $30,000 to $50,000 per workshop as a round number. Some are less and some more, depending on how many you have and how long they go on.

May I say, sir, that we have found a workshop exceptionally useful in areas many of which, as in autism, for example, we really don't have enough information available to know precisely where to go. We need to bring the experts together to crystallize, so to speak, the problem, and there is a spinoff from this, because when you bring these people together they effectively interact with each other, as shown in multiple sclerosis or in diabetes where we have had workshops.

Mr. MICHEL. Is it more meaningful than a full-blown kind of conference?

Dr. TOWER. Yes, sir, absolutely, because the people are able to get together intimately, they are not inhibited by an enormous room and enormous number of people. I don't mean to say they should be private but the interaction is much easier when you have smaller groups, and they go home charged up with a lot of new ideas. This has certainly occurred in the ones we have seen in the past, whether it's regeneration of the nervous system or diabetes or multiple sclerosis or whatever it is.

DIABETES

Mr. MICHEL. On that subject of diabetes, how much research are you doing, dollarwise in that area in your shop?

Dr. TOWER. Well, we have a figure that the Diabetes Commission has developed that at the present time, referring to fiscal 1975, the past year, of $1.365 million. Our problem is that in a sense everything we are doing is diabetes related, because the nervous system depends on an adequate supply of glucose and glucose supply is upset in diabetes, but that is not a very helpful way of looking at it. If you just look at the number of grants and other activities in which diabetes appears in the name, this comes up to be about $450,000, so perhaps $1.365 million is a reasonable compromise.

A great deal more of our basic research will be relevant to this problem. So that that is only the tip of the iceberg, in a sense, and we will add to this, particularly for the problem of diabetic neuropathy, as I indicated earlier. This needs more emphasis and the workshop that we and the Diabetes Commission organized last summer indicated where the needs are, and we are going after those.

Mr. MICHEL. It is good to get your response. I wish that during some of the debates on the floor of the House we could have your ready expertise at hand. Those of us who are laymen and get only what we really know on the firsthand basis, by way of these hearings, are not able to absorb it all within an hour or 2 hours' time, and we are getting such a proliferation over here on the floor of both the House and Senate, you know, and Members will equate specific dollar figures with diabetes, period, and it is so structured and so rigid that if it isn't really in that Institute with the primary responsibility for it, they say we are not doing anything.

After 20 years of hearing the testimony from NIH officials, we know there is so much cross-fertilization and intermix here that it is just

impossible at times to try and clearly define, set apart dollar for dollar any number of, or charge up to a particular disease research, and so on, and I think we need some help in that record, particularly if we get going too far afield here sometimes.

I would just as soon have some more voluntary contributions on the part of your experts there to let us know, because we don't know. I would be willing to wager that those who don't get the benefit of sitting around this table for a couple of months each year like we do know less than we do, and many of them are calling the shots, unfortunately, with a majority of votes.

TRAVEL

Doctor, turning to another issue, what accounts for your reduction in travel expenses? I am not criticizing, I was just interested in the reduction.

Dr. TOWER. Well, we are trying to hold more meetings in central places, so that we don't have to travel people so far. We are trying to minimize the number of meetings. It is very difficult because interpersonnel communication is important. But we are doing the best we can in this regard, and we have cut down on some of the activities as, for example, the perinatal project which is closing down, so this will cut down on the amount of travel.

OTHER SERVICES

Mr. MICHEL. That is the good news; now the bad news that other services are up 40 percent. Why is that?

Dr. TOWER. I will let Dr. Frederickson answer that, that goes to NIH centrally.

Mr. MICHEL. All right, Doctor, we just passed the buck.

Dr. FREDRICKSON. I can't specifically say where that 40-percent rise is going but I can assure that part of the increase is going into central services, from which this Institute benefits, as do all of the others, for maintaining the resources that they need in common in order to carry out their business.

Mr. MICHEL. Now, are we being had here a little bit? It is easy to call it other services, but in your overall position, looking over all of the Institutes, Doctor, do you take the position that you don't want to beef up this or that figure, and so you add at each one of these Institutes a little bit more here and there to get around what maybe we have denied you in one form or another?

Dr. FREDRICKSON. I don't think that is true.

Mr. MICHEL. I have to ask you that probing question.

Dr. FREDRICKSON. Mr. Mansfield points out to me that the other services increase includes costs of central services which support the intramural program, such as research animals, instrumentation, and material management. Program evaluation costs are also included in the other services increase. About 51 percent of the other services increase is for computer services related to the collection of data for the collaborative perinatal project and for direct costs of the intramural research program.

PEER REVIEW PANELS

Mr. MICHEL. Finally, Dr. Tower, I have been asking each of the Directors of each of the Institutes to answer a similar list of questions, having to do with peer review panels, and grants and contracts.

I won't take up the time of the committee here to repeat those, but will submit those for the record, and would appreciate your responses, just as extensively as you wish to make them, or as briefly as possible, but where special explanation is required, feel free to do so.

[CLERK'S NOTE: A consolidation of these questions and the answers from all of the Institutes appears in the testimony of the Office of the Director, NIH.]

STROKE

Mr. MICHEL. What about the number of strokes occurring? Is this up or down?

Dr. TOWER. Since stroke is not a reportable disease, the exact number of new strokes occurring is unknown. However, the best figures available from hospital admissions indicate that 500,000 to 600,000 people in the United States have new or recurrent strokes each year. There is no indication that the figure has changed meaningfully in the past few years. However, the mortality rate following stroke is definitely decreasing. A critical issue is to prevent or diminish permanent nervous system damage in order to increase the quality of life following stroke.

RESEARCH OF OTHER AGENCIES

Mr. MICHEL. To what extent is research in your field of concern also undertaken by other institutes and agencies in the Federal Government?

Dr. TOWER. While it is virtually impossible to give a quantitative statement about the overlap of research effort among different NIH Institutes and other agencies, perhaps it would be helpful to indicate that the programs of the National Institute of Neurological and Communicative Disorders and Stroke have overlapping interests with most of the Institutes at the National Institutes of Health plus the National Science Foundation, the Rehabilitation Services Administration, the Veterans' Administration, and the Food and Drug Administration.

The nature of the overlap in interest varies. The retina of the eye is an extension of the nervous system and so is of interest both to researchers in the Eye Institute and NINCDS. Nervous system and communicative disorders of the young and old are the concern of the National Institute of Child Health and Human Development, the National Institute of Aging, the National Institute of Mental Health, and NINCDS among others.

Particularly, different types of expertise are required in order to understand the basic mechanisms operating in the nervous system. Sometimes research efforts combining different disciplines are supported by a single institute through program project grants, research centers, or intramural laboratories; but research problems of broad scope are often divided into areas of particular interest to particular Institutes.

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There is a tendency to think that duplication of research effort is necessarily bad and wasteful, but it is often imperative that important experiments be confirmed in other laboratories by researchers whose approaches may differ and who are aware of different alternative hypotheses. As a matter of fact, because of the uncertainties of the frontiers of scientific knowledge, it is extremely difficult for two laboratories to exactly duplicate research results.

COORDINATION OF RESEARCH

Mr. MICHEL. What kind of coordinating mechanism do you have to coordinate your research endeavors with those of other Institutes?

Dr. TOWER. Research grants of interest in two separate Institutes are generally provided dual assignments by the referral office of the Division of Research Grants. This insures that the two organizationally distinct groups are aware of the other's interest and that the advisory councils of both Institutes consider them for program relevance and coordination. This is a formal mechanism.

The network of health scientist administrators ordinarily extends beyond the bounds of formal responsibilities of the Institutes. The community is sufficiently small that experienced administrators are aware of one another's research support activities, which results in a considerable amount of informal coordination.

Contract research is usually developed in response to a need assigned by Congress or developed by staff surveys which include a search of published literature, the Science Information Exchange, and a detailed search of NIH grant and contract files to determine ongoing research prior to the release of a request for a proposal. If a sister Institute has overlapping interest they are invited to participate either scientifically or financially with our program in the development and monitoring of the contract project.

Mr. MICHEL. Thank you.

Mr. NATCHER. Mr. Roybal?

Mr. ROYBAL. Doctor, under neurological diseases you indicate you had funded 67 clinical research centers, 700 regular research grants, and 30 contracts.

Dr. TOWER. Yes, sir.

CONTRACT FUNDING

Mr. ROYBAL. Is it necessary to farm this out on contract?

Dr. TOWER. Mr. Roybal, there are certain problems that are best dealt with by the contract mechanism, because we wish to specify a particular service or to obtain a specific result.

Let me give you a couple of examples. When we wish to test a new anticonvulsant drug at the clinical level, which is required before the drug can go on the market and be available to all physicians, we need certain things done in testing that drug: How many patients with different kinds of epilepsy, how long, what kinds of epilepsy, what kinds of monitoring procedures we want, as for example, following the blood levels of the drug so we know that the patient complied, that they took the drug and had an adequate level to get a response, and so on.

This is very difficult to do by a grant mechanism, because it is not looked upon by the study sections as the type of research that they usually review and often it doesn't command a very high priority from them, but it is very essential information for us and the FDA to have before we can introduce a drug into the marketplace. So that we generally will run this type of study under contract.

Another example is if you need to acquire a certain service. For example, we have a very large program that deals with slow and latent viruses of the nervous system.

This requires our holding a large number of animals, who have been infected with various agents, and the reason that it is expensive is because they are slow viruses, they take many months or even years before they show up clinically. The only way we have of testing, is to inject these animals, so we have a contract out for holding animals because we don't have the facilities at NIH to hold animals. This gives you the extremes in contracting, and there are many other things.

You heard earlier about an implant for stimulators and electrodes and so forth. Many of these are not commercial organizations, they are universities and clinics and hospitals. For the epileptics, much of the drug evaluation is done at New Castle State Hospital out in Indiana where they have a very fine facility, with a resident population of epileptics that has been extremely useful in developing the drugs.

TYPE OF CONTRACTS

Mr. ROYBAL. You anticipated my next question. I wanted to know how many of these you are contracting to commercial firms?

Dr. TOWER. Actually, relatively few. We have some obviously to commercial firms, but relatively few of them. In actual fact, the majority are with nonprofit organizations.

Mr. ROYBAL. Do these commercial firms eventually benefit from their own research in the marketing of the medication?

Dr. TOWER. To some extent, but not as much as you might expect. Many epileptic drugs, for example, are not moneymakers, and that has been one of the problems. Patients need them, but they don't make money for the pharmaceutical companies and it is hard for us to encourage the pharmaceutical companies to develop them.

DRUGS

Mr. ROYBAL. Didn't you tell the committee a while ago that some of the drugs being developed are very expensive and cannot be afforded by people in lower income brackets or even middle-income brackets?

Dr. TOWER. Yes, sir, they are complicated compounds to make, they are not easy to make.

Mr. ROYBAL. You mean there is very little profit in it?

Dr. TOWER. There is very little profit because the market is not large. If you compare the market for epileptic drugs with the market for, say tranquilizers as a general class, we are talking about a few million patients versus hundreds of millions.

Mr. ROYBAL. Yes; but there are also hundreds of firms engaged in producing tranquilizers.

Dr. TOWER. Yes, sir, but it is a much more lucrative market than the epileptic drug market because, while we have 2 million to 4 million epileptics in this country, not all of them will be taking any given drug, so that you have very small portions. No matter what drug you develop, it is going to be best for some epileptic patient, but it's not commercially profitable to keep manufacturing it.

Mr. ROYBAL. How can these drugs be made available to people in lower income groups?

Dr. TOWER. Well, there have been a number of proposals. I wouldn't like to make a suggestion here, but simply to point out that some people have felt they should be made available free to those who can't afford them through some mechanism, medicare or medicaid or special provisions of social security or other areas or they should be available on a partial cost.

There are a number of mechanisms that are available that have been suggested, and I simply don't know enough about that area to suggest which would be the best.

Mr. ROYBAL. Well, it just seems to me the delivery system is geared to the wealthy, and only the wealthy.

Dr. TOWER. Well, Mr. Roybal, I am afraid that is a specific example of the fact that most of us can't afford to get sick. This is the real problem.

Mr. ROYBAL. People do get sick regardless of their personal income, and those who are in the lowest of income brackets are the ones that seem not to be getting the benefit of all of this research in spite of all the money that is being made available by the Government for this specific purpose.

Dr. TOWER. Well, Mr. Roybal, you are discussing a problem now where we at the NIH have a considerable amount of difficulty, because you are getting at the interface between what research accomplishes and the delivery of this to the patients. I believe that it is fair to say that the NIH can only go so far with this, because we not only do not have the resources and the manpower to deal with this problem, but I think we get to areas which are legitimately the concerns of other peopel and other agencies. One must deal with the entire spectrum, there is no question about that. That is why I hope, in the specific example of epilepsy, that the comprehensive programs we are developing will give some of the answers as to how best to deal with the interface. That is one of the major points of having these comprehensive epilepsy programs.

Mr. ROYBAL. But you do agree that this is a problem?

Dr. TOWER. Absolutely, no question about it.

TRAINING GRANTS

Mr. ROYBAL. One thing I cannot understand is while all of this is going on, you are still terminating training grants for neurological disorders. Now, isn't a training grant more directed to the rank and file than it is to those than can really afford a service?

Dr. TOWER. I am not sure I understand the question, Mr. Roybal.

Mr. ROYBAL. What are you terminating with regard to training grants?

Dr. TOWER. Well, these, that we are terminating, sir, are the so-called old training grants that we had for many years. The decision was made by the department a couple of years ago, 3 years ago, that this program should be phased out, and for it has been substituted the new National Research Service award training program.

Mr. ROYBAL. What is a training grant now? Who do you train?

Dr. TOWER. A training grant in our context, sir, is a grant to a university hospital, or similar institution of that sort; in this case it would be to one of the neurological or communicative disorders departments which would receive money.

Under the old system they would get money not only for the stipends for the fellows that would be trained, but also for equipment, salaries, and other things for the staff of the institution that would be needed to provide the adequate environment for such a training situation.

Mr. ROYBAL. But you would train more people in the field that would ultimately reach out into the communities.

Dr. TOWER. Well, our authority for training is limited to training researchers and academicians. It is not designed to train practitioners. That is a different responsibility that belongs to the Health Manpower Agency.

Mr. ROYBAL. I thought you were discontinuing the training of individuals who became experts in the field and ultimately be made available to people in the lower income brackets. And that is not the case.

Dr. FREDRICKSON. Well, they will in the sense that what knowledge they generate will certainly spread throughout the system. They will also often be operating in the larger medical centers where the care of those in the lower income brackets is frequently a very important part of the activities.

Mr. ROYBAL. Yes; I doubt that essentially these people would be the recipients of that knowledge. But the costs that have been indicated, it is going to be pretty difficult for people in lower income groups to really benefit from all of this work.

Dr. FREDRICKSON. I think it should be pointed out, Mr. Roybal, that many of the drugs that you mention, for example, are certainly available to the lower income groups through both medicaid and medicare programs. It is really a question of which third party is to cover the cost of these; but, in many instances, medicaid will be.

Mr. ROYBAL. Not all of these people are 65 years of age and over.

Dr. FREDRICKSON. But medicaid is for individuals younger than 65.

Mr. ROYBAL. I understand, but if you have been through that process you know how difficult it would be to even get some of the drugs paid for by that particular system.

Dr. FREDRICKSON. Yes, sir.

TRAUMA AND ACCIDENTS

Mr. ROYBAL. Now on another field that I am interested in, the Institute indicates that direct trauma from accidents, especially traffic accidents, is increasingly alarming as a cause of cerebral palsy. What data can be presented to this committee concerning the situation?

For example, how many are suffering from cerebral palsy as a result of traffic accidents? Are there any statistics with regard to this?

Dr. TOWER. I don't think we have very good statistics, sir; no. As you know, cerebral palsy is a rather general term. It has been most traditionally applied to children who suffer neurological defects and trauma at birth or as a result of infectious or other diseases in early childhood. But cerebral palsy is a term that is applied to a constellation of symptoms which can occur at any age, and automobile accidents or other accidents which involve the nervous system can produce the constellation of symptoms which can be characterized as cerebral palsy.

To give you precise numbers, I am not sure I could do that, but I will be glad to try and supply what information we have for you. I don't have that information at my fingertips. We have a fair amount of research going on as to what the mechanisms of injury are, and how we may minimize these.

[The information follows:]

ACQUIRED CEREBRAL PALSY

Analyses of possible causative factors relating to cerebral palsy is now underway in the National Institute of Neurological and Communicative Disorders and stroke collaborative perinatal project. Preliminary results indicate that 10 percent of cerebral palsy is caused by events occurring after the first month of life. Of such acquired cerebral palsy recognized in the collaborative project, approximately 40 percent could be related to infections of the brain and its covering membranes, 35 percent to physical trauma. The remainder of acquired cerebral palsy was apparently related to toxic disorders of underlying cardiovascular or blood abnormalities.

In a subgroup of children with marked cerebral palsy who also had severe mental retardation, 14 percent acquired their defects after the first month of life. In this severely handicapped group, 8 percent had infectious origin, and 4 percent had suffered physical injury. Of the total group with cerebral palsy and severe mental retardation, 3 percent had metabolic disorder, 2 percent chromosomal abnormalities, 14 percent structural abnormalities of the brain, and 8 percent infections in pregnancy or within the first month of life.

HEAD INJURY

Dr. TOWER. For example, we have had for a number of years a contract from the Department of Transportation to carry out experimental studies on head injury, to provide the Department of Transportation with information that they could use in a better design of helmets, for example, for motorcyclers. The military is interested in the helmets for various types of activities they are involved in. Much of the information on whiplash was developed through these studies and so on. The result of such injuries may produce a so-called cerebral palsy individual, so this is the type of approach we are taking on the one hand of trying to minimize or prevent these, and then on the other hand, we are dealing with questions of how to restore function afterward, and this gets us into, for example, regeneration of the central nervous system, where we are investing quite a lot of research to try to learn how to put back function again to those areas which have been knocked out.

Mr. ROYBAL. But that would be a fascinating field, I would think, to research.

Dr. TOWER. Yes, sir; it is extremely important, because the largest single cause of death and disability among young people, and I am talking about the age between about 10 and 30 years of age, are accidents, and 70 percent of those accidents are calculated to severely involve the nervous system. So it is a very big problem, and a very important one.

CHILD ABUSE

Mr. ROYBAL. We constantly read in the newspaper of children being abused and neglected and so forth. Is there any relationship between child abuse, neglect, and cerebral palsy?

Dr. TOWER. I am not really sure I can answer that question for you. You are getting a little bit beyond the border of our responsibility because child abuse gets into the area of the Mental Health Institute and to some extent the Child Health Institute.

But clearly children who are not normal, and I am not sure we want to define that too closely, may not generate in certain parents—particularly at the lower income levels where the educational opportunities have been less than optimal—those children may not react well with the parents. We have examples from other cultures, particularly in areas of the developing world, where malnutrition is a very serious problem, much more so than in this country, where neglect of the child is a very common component of the malnutrition syndrome. In fact, certain studies carried out in Central America have indicated that this may be the most important component, and that it really isn't the malnutrition, but it is the fact that parents tend to neglect these children; they don't get brought into the activities and the communications that are normally necessary for the growing youngsters to acquire language, and speaking skills, the skills that a young child must learn, so there is no question this is an important problem.

Mr. ROYBAL. Now, isn't your Institute at the moment in cooperation with the Institute of Child Health and Human Development studying this problem?

Dr. TOWER. We are not studying the abused child, no, sir. I believe that would be between Mental Health and Child Health.

Mr. ROYBAL. But someone is studying it.

Dr. TOWER. Yes, sir, absolutely.

Mr. ROYBAL. I was under the impression that you, in cooperation with the Child Health and Human Development Institute, had started studies along this line and I just wanted to know how far advanced you were and what you have learned, because this is also a very important subject.

Dr. TOWER. We will get this information for you. It has not been part of our responsibility, but we will be glad to provide a bit about what is going on and who the people are.

[The information follows:]

CHILD ABUSE

The National Institute of Child Health and Human Development is supporting research and training grants which are relevant to child abuse and neglect. These projects, currently supported at a level of about $350,000, deal primarily with maternal-infant interactions: studies on how an infant's reaction or response to his or her parents influences the relationship between the parents and the

child; how the parent-child interaction affects the infant's emotional, social, and cognitive development. By knowing the factors which influence normal interaction between the parents and the child, it will be possible to detect deviant behavior which may lead to abnormal parent-child interaction which could result in child abuse.

In addition, the National Center for Child Abuse and Neglect, an agency of the Office of Human Development, conducts research intended to improve detection of child abuse and to improve treatment of abused children and underlying family conditions. The Center's programs are authorized by the Child Abuse Prevention and Treatment Act. The Department's child abuse programs are coordinated by an interagency staff committee: the Advisory Board on Child Abuse and Neglect.

Mr. ROYBAL. I would also ask the question of the appropriate agency when it comes before us.

Again, I think this is a field that is most interesting. It is to me and I am sure it would be most interesting to people who work with children throughout the United States.

That is all, Mr. Chairman. Thank you very much.

Mr. NATCHER. Doctor, since our chairman, Mr. Flood, could not be here today he asked me to present you with a list of questions on multiple sclerosis that you can answer for the record.

[The information follows:]

MULTIPLE SCLEROSIS

Question. Dr. Tower, the Multiple Sclerosis Commission recommended that you make one member of your staff administratively responsible for all NINCDS-funded research on MS and perform these other activities as described on pages 126–128 as described in volume 2 of the Commission's report. Please advise of your reaction to this recommendation and the response you have made to it.

Answer. Dr. John Sever, the chief of the infectious diseases branch of our intramural research program, has been involved in microbiologic studies on multiple sclerosis for several years. He is knowledgeable about the many efforts underway relative to the MS problem. He has been identified as the Institute focal point for MS issues. He is also a member of the National Multiple Sclerosis Society's Medical Advisory Board. Further, we are seeking a suitably qualified health scientist administrator to manage our extramural program related to multiple sclerosis and other demyelinating diseases. When this person is at work, he or she will provide, with Dr. Sever, a vigorous and adequate coverage. We do not believe a full-time staff member with specific responsibility would provide a more effective response to the problem.

Question. The Commission recommended that there be established a multidisciplinary study section MS to operate in the manner described on pages 128–134 of volume 2 of the Commission's report. Please explain in some detail the specific actions you have taken on this recommendation.

Answer. The creation of study sections is the responsibility of the Office of the Director, NIH. The Office of the Director retains responsibility for the initial review of research grants. NIH has traditionally organized study sections on a disciplinary basis—anatomy, medical chemistry, neurology, etc.—not on the basis of specific diseases. We tend to support this policy for a number of reasons. I would say that when NINCDS has responsibility for initial review—for contracts, program projects, and other special cases—we convene review panels specially selected to assure the most fair and objective review possible. Interdisciplinary initial review groups are the rule rather than the exception for projects related to MS reviewed in this manner.

Question. The Commission stated "that one of the greatest unmet needs in multiple sclerosis is a suitable mechanism to encourage interdisciplinary planning and pursuit of research directed to obtaining definite answers to important and relevant questions." The specific suggestions relating to this new approach can be found on pages 136–140 of volume 2 of the Commission's report. Please indicate specifically whether you agree or disagree with this approach and what specific steps, if any, you have taken to implement this recommendation.

Answer. We believe that the Institute, through the laboratory and clinical studies of its intramural research program, individual research grants, and

center grants, a continuing series of small meetings and workshops, and targeted research supported by contract, has indeed implemented an effective interdisciplinary coordinated collaborative-cooperative attack on multiple sclerosis. We have cooperated completely with the National Multiple Sclerosis Society, sharing with them information on active grant programs and other ongoing research projects. Members of our staff have served and will continue to serve on the Medical Advisory Board of the Multiple Sclerosis Society when they are asked to do so. We believe that these mechanisms of coordination are as effective as those specifically recommended by the Multiple Sclerosis Commission and are responsive to the sense of the Commission's recommendation.

Question. I believe one suggestion was to make use of this approach in developing a drug for use in MS. Have you discussed with appropriate officials of the National Multiple Sclerosis Society the possibility of collaboratively supporting such an endeavor? If so, what reaction did you encounter?

Answer. Over the past 2 years NINCDS grantees have undertaken studies of the use of immunosuppressive drugs to treat MS. These studies are based on the hypothesis that MS is caused by a deficiency in the body's immune responses, triggered by some type of virus infection. Some of this work has been done by scientists at the Wistar Institute of Philadelphia which has an NINCDS program project grant for MS research, and also support from the Multiple Sclerosis Society. Unfortunately the results of these studies of immunosuppressants have not yet shown promise. We know that the Multiple Sclerosis Society is supporting other drug studies as well, but to my knowledge, our staff has not been approached by nor have we approached the society concerning joint studies because the opportunities for this type of research are not promising. If our or the society's preliminary efforts uncover important leads, we would be prepared to vigorously pursue them. I should note that our staff has been in contact with staff and grantees of the society since 1974 and have discussed the scientific aspects of drug research extensively.

Question. Although many of the other recommendations of the Commission are of some considerable interest to me. I would particularly call your attention to recommendation No. 13 on page 181 of volume 2 of the Commission's report. Would you in this instance identify the grants or contract(s) or the intramural scientists who are pursuing this recommendation so that I could see which scientists and how much money is being directed by NINCDS to this particular suggestion?

Answer. Although no specific studies of the initial covert signs of multiple sclerosis have been undertaken, a major effort of the study of the epidemiology and serology of MS in the Shetland and Orkney Islands of the United Kingdom is an attempt to identify any common phenomena in this location where the incidence of MS is abnormally high. The data collection and certain data analyses for this study are being conducted under contract with the Massachusetts General Hospital, the principal investigator being Dr. David Poskanzer. It is being closely monitored by Dr. Bruce Schoenburg an NINCDS neuro-epidemiologist. Dr. John Sever has done the serological tests on blood samples from the study patients, while Dr. Paul Terisaki of the University of California at Los Angeles is to do studies of certain blood antigens. Dr. Derek Roberts of the University of Newcastle upon Tyne is performing the genetic studies. Data analyses are already underway under the direction of Mr. William Weiss, chief of the NINCDS Office of Biometry and Epidemiology. Until some clues are provided by this study, we believe more specific investigation would be ineffective. NINCDS has invested over $300,000 during the past 3 years in this study. An additional $150,000 will be spent to bring the study to a successful close.

Another such study is being conducted by Dr. Henry McFarland of the NINCDS Laboratory of Neuroimmunology who is engaged in tissue and histocompatibility studies in families in which there are affected and nonaffected members who are being compared. One such cluster of families being studied is located in Milwaukee, another in Wichita, Kan. Dr. John Sever is also carrying other studies in these same groups of families.

Question. Finally, would you give me the present annual level of funding of MS research by NINCDS? I want this annual level of funding to include extramural grants, the cost of intramural research and the amount of any appropriate contracts.

Answer. NINCDS expects to be able to meet or exceed the funding levels recommended by the National Advisory Commission on Multiple Sclerosis in its 1974 report for both fiscal years 1976 and 1977. In 1976, the forecast investment in-

cludes 55 research grants, including 5 clinical research centers, 8 contracts, and 24 intramural research projects at NINCDS, for a total investment of $9.59 million compared to the $8.99 million recommended by the Commission. We anticipate a modest increase in multiple sclerosis research funding for 1977 to an estimated $11 million compared to the $10.16 million recommended by the Commission.

The NINCDS has just prepared a report giving in summary and quantitative form the current status of this Institute's response to the Commission's recommendations. I think it fair to say that the major advance has been the stimulation in interest in the multiple sclerosis problem within many facets of the biomedical research community. This heightened interest clearly results from the stimuli provided by the Commission and by the funding opportunities afforded by NINCDS and the National Multiple Sclerosis Society. I am confident that we may expect continued progress in unravelling this most perplexing clinical problem.

[The material referred to follows:]

CURRENT STATUS OF NINCDS RESPONSES TO RECOMMENDATIONS OF THE NATIONAL ADVISORY COMMISSION ON MULTIPLE SCLEROSIS

Introductory Note.—The Commission report (submitted in Feb. 1974) contains recommendations (Vol. II, pp. 174–192), only a very few of which specifically mention NINCDS. Moreover these are recommendations only, and should not be viewed as mandatory or inflexible. In many cases throughout the report, the role of the National Multiple Sclerosis Society is also stressed, and on page 172, paragraph *a*, it is noted that in 1973 the Society funded research at a level of almost $2 million, or about 38 percent of the total support for that year. This source of funding has been sustained, and in fact for one NINCDS grant (to Koprowski at the Wistar Institute), the MS Society supplemented the NINCDS funds with a substantial input of their own for projects which the NIH Study Section recommended that the NINCDS not fund. Thus the Commission recommendations should be viewed, in my opinion, as applicable to all agencies, public and private, responsible for research on MS. This does not lessen the moral responsibility of the NINCDS as the relevant principal Federal agency, but it does put the matter in proper perspective. One other caveat is important. An overemphasis on funding per se seems to me to be wrong. What we must be concerned with is the research progress—the acquisition of new knowledge and the advancement of our understanding of MS—not whether we have spent more or less than the number of dollars recommended by the Commission.

I. *Funding by NINCDS for MS related research, fiscal year 1974–fiscal year 1977* (cf. pp. 174–176).

[In millions of dollars; fiscal years]

	1974	1975	1976	1977
Appropriations	[1] 121.3 [143.5]	142.4	144.7	146.5 [P.B.
MS Commission: Base funding	[2] 3.15	3.15	3.15	3.15
Recommended addition [3]		3.86	5.84	7.01
Actual NINCDS obligations		6.98	[4] 9.59	[5] 11.06

[1] Figure in brackets includes impounded funds from fiscal year 1973 released for obligation in fiscal year 1974.
[2] Actual.
[3] Excludes the $12,000,000-plus recommended (annual) as additional funds for basic research. Congress did not act on this recommendation directly or comment on it in their reports.
[4] Breakdown: 55 grants (including 5 centers) at $6,510,000; 8 contracts at $63,000,000; and 24 intramural projects at $2,450,000.
[5] Estimated.

NOTE.—No NINCDS act is warranted on the basic research recommendations A and B on pp. 175–176, nor on recommendations a and b on p. 176. These are directed at the Congress or at the NIH.

II. *Specific Research Recommendations* (pp. 176–188):

	Fiscal Year 1976
1. Additional clinical research centers:	
Response. Centers now being funded:	
UCLA (Wolfgram) from fiscal year 1971	$350,000
University of Pennsylvania (Silverberg) from fiscal year 1974	310,000
Emory (Kibler) fiscal year 1974 [1]	270,000
St. Vincent (Bartfeld) fiscal year 1975 [1]	300,000
Yeshiva (Bornstein) fiscal year 1975 [1]	650,000
	1,860,000
Plus program projects:	
Wistar (Koprowski) from fiscal year 1974	490,000
Scripps (Oldstone) fiscal year 1975 [1]	240,000
	730,000
Totals	2,590,000
Recommended	750,000
2. NINCDS to support source for fresh MS tissue:	
Response. Contract being negotiated with Dr. W. W. Tourtellotte (Wadsworth VA Hospital., Los Angeles) to supplement existing frozen tissue bank. Joint NINCDS–NIMH support (year)	59,000
Recommended	60,000
3. Isolation of infectious agents in MS:	
Response. A major EP and IR effort now in progress (in part)	1,700,000
Recommended	750,000
4. Repeated paired samplings of blood and CSF:	
Response. Several studies EP and IR underway	>500,000
Recommended	140,000
5. Incomplete virus studies:	
Response. Major IR effort, plus several EP studies (and a number not funded by NINCDS)	>350,000
Recommended	240,000
6. Autoimmunity studies:	
Response. Oldstone center plus IR studies	170,000
Recommended	170,000
7. Minimization of cross-contamination:	
Response Budget items for most EP centers; major items of renovation for IR	>2,000,000
Recommended	150,000
8. Body fluid studies for diagnostic tests:	
Response. IR projects and contracts, plus studies at EP centers	>$250,000
Recommended	250,000
9. Usefulness of CAT and proton-beam brain scans:	
Response. Numerous centers doing routinely (notably Mayo and MGH) with equivocal results at best; IR (Di Chiro) working on proton-beam	?
Recommended	$83,000
10. Collaborative development of immunosuppresive or anti-inflammatory drugs for MS:	
Response. NINCDS workshop in 1975 on current status. No NINCDS program. MS Society has a program.	
11. Efficacy of various therapeutic regimes:	
Response. Several grantees (Wolfgram, Cole, Zabriskie, Arnason) evaluating immune sera, immunosuppressive, transfer factor, etc	>$300,000
Recommended	278,000

[1] Funded since MS Commission report.

12. CSF gamma globulin and antibody levels:	
Response. Active work in all EP centers as well as IR (in part)	$2, 700, 000
Recommended	200, 000
13. Retrospective evaluation of initial covert signs of MS:	
Response. Part of various ongoing studies including Orkney-Shetland survey (see No. 26 below) and family studies by IR.	
14. MS Clinical Treatment Center:	
Response. Not within NINCDS mission to fund a service facility. MS Society has under consideration.	
15. Correction of transmitter defects:	
Response. Large effort in synaptology and transmitters; specific IR studies plus several EP grants	>$150, 000
Recommended	150, 000
16. Cell-mediated immunity studies:	
Response. Extensive studies at all EP centers by many IR units and other EP grants (in part)	$2, 800, 000
Recommended	100, 000
17. Histocompatibility antigen studies:	
Response. Extensive IR and EP studies (in part)	$1, 150, 000
Recommended	250, 000
18. Factors in exacerbations of MS:	
Response. Some IR and EP center studies:	
1 specific grant (in part)	$400, 000
Recommended	250, 000
19. Comparative analyses of brain cells:	
Response. Much routine morphological study in all EP centers and in IR; isozyme studies not common	?
20. Tissue cultures of oligos and lymphocytes:	
Response. Studies in most EP centers (about)	1, 000, 000
Recommended	148, 000
21. Unique markers for culture cell lines:	
Response. At least 4 studies underway	>$200, 000
Recommended	50, 000
22. Mechanisms of long-term viral persistence in brain:	
Response. Major aspect of IR projects and many EP grants at at least 10 times the recommendation	>$2, 500, 000
Recommended	240, 000
23. Model for de- and remyelination:	
Response. Both IR and several EP projects	>$300, 000
Recommended	300, 000
24. Study of MS sera as demyelinators:	
Response. Work at at least 3 EP centers as well as IR (in part)	$1, 280, 000
Recommended	250, 000
25. Indicators to monitor stages of MS:	
Response. 2 workshops in 1975 (most group working on this)	>100, 000
Recommended	200, 000
26. Evaluate Orkney-Shetland Is: focus of MS:	
Response. Contract entering 3d year at total	>300, 000
Recommended	100, 000
27. Two possible additional epidemiological studies:	
Response. Chile—proposal disapproved at TMR	
U.S.S.R.—exchange mission in May 1975 (with Director, NINCDS as member). A followup through WHO is proposed.	
28. Study of MS clusters:	
Response. Studies in 3 areas underway by IR. (Also MS survey underway by NINCDS–OBE.)	>$25, 000
Recommended	25, 000
29. Suitable studies of EAE:	
Response. At least 5 EP grants plus IR studies	>$270, 000
Recommended	20, 000

III. *Recommendations on Organization and Management* (pp. 188–192)

(a) Full-time NINCDS staff member:

Response. Dr. John Sever designated in February 1974 as focal point. The Director, NINCDS disagrees with the specific Commission recommendation and will not comply in that specific way. It is managerially objectionable and he lacks sufficient slots. Plans have already been made for an appropriate branch in the neurological disorders program.

(b) Establish an MS Study Section:

Response. Not an NINCDS responsibility but disagree completely anyway.

(c) NINCDS to launch interdisciplinary coordinated, collaborative, cooperative attack on MS:

Response. IR programs; EP centers; workshops.

(d) NINCDS to collaborate with MS Society to produce indicative abstracts on MS:

Response. NINCDS decision not to fund because of limited resources for such information services, especially for individual disease coverage. NINCDS funds two general information networks that include MS-relevant citations. MS Society is funding the indicative abstracts.

(e) Data bank for cross-referencing grants and contracts:

Response. Not NINCDS responsibility. However, do provide to MS Society semiannual computer runs of all grant, contract, and IR projects in force.

(f) Commission indepth reviews on three topics:

Response. Viral cause of MS—written and funded by NINCDS. Biochemistry of myelin—MS Society responsibility. Survey of EAE—not yet initiated by NINCDS.

(g) DHEW to provide more realistic fellowship stipends:

Response. Not NINCDS responsibility but we concur.

(h) DHEW to provide for additional biomedical research manpower positions in United States:

Response. Not NINCDS responsibility but we concur.

(i) Monitor measles—vaccinated population for MS:

Response. Preliminary work underway by IR scientists and some EP centers.

(j) NINCDS budget to be finalized before fiscal year begins:

Response. Not NINCDS responsibility but we concur.

(k) Cooperation of NINCDS and MS Society:

Response. There is currently regular exchange of funding and project title information. Grant support has been shared in one major instance. Numerous IR staff serve on MS Society committees. An MS Society officer is currently a member of the NINCDS Council.

SUMMARY

In summary it is our collective opinion that the NINCDS has been more than responsive to the Commission report and recommendations. More importantly the biomedical community has responded to the task force meetings held by the Commission and subsequent workshops with an enthusiastic outpouring of ideas and grant applications; so that a real increase in research effort is underway across the country and around the world. It is important to caution against overoptimistic expectations of quick results. MS is an extraordinarily complex disorder, and our increasing recent knowledge adds to that complexity. Progress toward prevention, specific diagnostic procedures, and effective therapies is likely to be slow for some time to come.

COMMUNICATIVE DISORDERS

Mr. CONTE. Dr. Tower, what is the most prevalent type of communicative disorder, and what percentage of your budget is devoted to it?

Dr. TOWER. The most prevalent type of communicative disorders are the speech disorders. A very conservative estimate is that 5 percent of the total U.S. population of all ages has some type of speech disorder. Approximately 10.6 percent of the budget for research support in our communicative disorders program is devoted to research on speech disorders. This can be estimated, very roughly, to be 1.7 percent of the total budget for research support of the Institutes.

RESEARCH GRANTS

Mr. CONTE. On page 197 of the justification I noticed that there is proposed, a $744,000 decrease in regular research grants and an increase of $1,454,000 in special grants. Would you explain the difference between the two and why changes in funding?

Dr. TOWER. The regular research grant activity provides funding for individual research projects. These projects generally are investigator initiated. The special grant activity includes the clinical research center program of the Institute and the research career development award program. These programs comprise targeted research efforts in special areas of high program relevance such as stroke, head and spinal cord injury, multiple sclerosis, and deafness. The decrease in regular research grants reflects essentially an administrative reclassification of grants, and not an actual change in funding levels. The reclassification permits us to more accurately monitor these activities.

HEAD INJURY

Mr. CONTE. I have been pleased to see the results that the emergency medical services program has had, it is a good effort. Has your Institute done anything on head injuries in conjunction with EMS?

Dr. TOWER. The working relationship between emergency medical services and the National Institute of Neurological and Communicative Disorders and Stroke has involved coordination of activities in the area of central nervous system trauma and particularly spinal cord injury. A multiagency effort on nervous system trauma involving the NINCDS, the EMS, and the Rehabilitation Services Administration is now in the preliminary planning phase.

INFORMATION ACTIVITIES

Mr. CONTE. How much do you spend annually on information activities?

Dr. TOWER. Last year, apart from personal services, NINCDS spent $82,000 for information activities.

Mr. CONTE. How large and what type audience receives this information?

Dr. TOWER. A wide audience from every State receives NINCDS information including Members of Congress, staff of the Department of Health, Education, and Welfare, and other Federal and State agencies, scientists, physicians, professional societies, voluntary agencies, and the general public. The information supplied last year included health education materials for the public, scientific information for scientists and physicians, and videotaped continuing education materials for scientists and physicians. Some 2,200 requests for continuing education material were received from 36 States, District of Columbia, Puerto Rico, and Canada, from medical schools, hospitals, rehabilitation centers, clinics, professional societies, and physicians. Last year over 3,000 public inquiries, including congressional letters, were received from every State requiring individually written letters to answer specific questions about neurological and communicative disorders. In addition, NINCDS responded to requests from scientists, physicians, and the general public for more than 400,000 copies of our publications relating to specific disease categories and to recent research findings.

Mr. NATCHER. Doctor, it has been an excellent presentation. Thank you.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Amounts Available for Obligation 1/

	1976	1977
Appropriation	$136,546,000	$146,532,000
Request pending	7,900,000	---
Subtotal Adjusted Appropriation	144,446,000	
Comparative transfer from:		
"Office of the Director, NIH" for Standard Level User Charge	261,000	---
Total, obligations	144,707,000	146,532,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $100,000; 1977 - $100,000.

National Institute of Neurological and Communicative Disorders and Stroke

Budget Mechanism

	1976 Estimate			1977 Estimate		
	Number	FTE 1/	Amount	Number	FTE 1/	Amount
Grants						
Regular						
Non-competing	923	--	$65,000,000	850	--	$60,126,000
Competing	179	--	12,226,000	203	--	13,977,000
New	126	--	6,578,000	150	--	8,118,000
Supplemental	(55)	--	1,000,000	(55)	--	1,000,000
Subtotal	1,228	--	84,804,000	1,203	--	83,221,000
Special						
Specialized Research Centers	--	--	7,308,000	--	--	9,492,000
Scientific Evaluation	--	--	255,000	--	--	312,000
Research Career Program	103	103	2,277,000	110	110	2,445,000
Subtotal	103	103	9,840,000	110	110	12,249,000
Total Grants	1,331	103	94,644,000	1,313	110	95,470,000
Fellowships						
Non-competing	176	225	2,891,000	154	208	2,645,000
Competing	--	--	---	--	--	--
New	55	55	609,000	163	163	1,796,000
Supplemental	--	--	600,000	--	--	900,000
Subtotal	231	280	4,100,000	317	371	5,341,000
Training Grants						
Non-competing	52	177	3,800,000	--	--	--
Competing	--	--	--	--	--	--
New	--	--	--	--	--	--
Supplemental	--	--	--	--	--	--
Subtotal	52	177	3,800,000	--	--	--
Intramural Research and Direct Operations	--	--	30,782,000	--	--	33,897,000
Research and Development Contracts	66	--	10,835,000	69	--	11,191,000
Program Management	--	--	285,000	--	--	295,000
Standard Level User Charge	--	--	261,000	--	--	338,000
Total	--	--	144,707,000	--	--	146,532,000

1/ Full-time equivalents

69-536 O - 76 - 31

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1977 JUSTIFICATION

INSTITUTE: National Institute of Neurological and Communicative Disorders and Stroke
(Dollars in thousands)

Mechanism / Program	Research Grants						Intramural Research and Direct Operations	Research and Development Contracts	Program Management	Total
	Regular Program		Specials		Training Programs					
	Non-Competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Communicative Disorders.....	11,843	2,744	150	205	867	811		1,436		18,056
2. Neurological Disorders.....	34,582	12,277	2,764	1,762	2,388	2,988		7,631		64,392
3. Stroke and Nervous System Trauma.....	8,487	1,898	4,044	168	258	134		1,018		16,007
4. Fundamental Neurosciences....	10,088	2,885	350	397	287	167		750		14,924
5. Intramural Research and Direct Operations							31,043			31,043
6. Program Management.....									285	285
Total obligations.....	65,000	19,804	7,308	2,532	3,800	4,100	31,043	10,835	285	144,707

DHEW - National Institutes of Health

CROSSWALK - 1977 COLUMN 1977 JUSTIFICATION

INSTITUTE: National Institute of Neurological and Communicative Disorders and Stroke
(Dollars in thousands)

Mechanism / Program	Research Grants						Intramural Research and Direct Operations	Research and Development Contracts	Program Management	Total
	Regular Program		Specials		Training Programs					
	Non-Competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Communicative Disorders.....	10,343	3,464	450	277	--	1,050		1,483		17,067
2. Neurological Disorders.....	34,105	12,010	4,060	1,920	--	3,999		7,882		63,976
3. Stroke and Nervous System Trauma.....	5,947	3,926	4,682	157	--	138		1,052		15,902
4. Fundamental Neurosciences....	9,731	3,695	300	403	--	154		774		15,057
5. Intramural Research and Direct Operations.....							34,235			34,235
6. Program Management									295	295
Total obligations....	60,126	23,095	9,492	2,757	--	5,341	34,235	11,191	295	146,532

Summary and explanation of changes

1976 Estimated obligations	$144,707,000
1977 Estimated obligations	146,532,000
Net change	+1,825,000

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Increases:				
A. Built-in:				
1. Annualization of 1975 pay increase	--	$494,000	--	+$191,000
2. Within grade salary increases	--	262,000	--	+306,000
3. Postage rate increase	--	201,000	--	+35,000
4. Bureau of Employees Compensation increase	--	21,000	--	+4,000
5. Service and supply fund increase	--	1,630,000	--	+263,000
6. Federal Telecommunications rate increase	--	85,000	--	+26,000
7. Program evaluation and general expense increase	--	1,700,000	--	+300,000
8. Payment to NIH management fund	--	8,264,000	--	+940,000
9. Standard Level User Charge	--	261,000	--	+77,000
Subtotal	--	--	--	+2,142,000
B. Program:				
1. Research Grants:				
a. Non-competing from awards in prior years	--	72,921,000	--	+25,786,000
b. Research grants, new and competing	--	21,221,000	--	+4,800,000
2. Fellowships (NRSA)	--	3,865,000	--	+1,422,000
3. Research and development contracts	--	10,835,000	--	+356,000
4. Intramural research and direct operations	--	30,782,000	--	+1,137,000
Subtotal	--	--	--	+33,501,000
Total, increases	--	--	--	+35,643,000
Decreases:				
A. Built-in:				
1. One less day of pay	--	13,256,000	--	-44,000
Subtotal	--	--	--	-44,000
B. Program				
1. Decrease of 32 positions from 1976	543	33,000	-32	-33,000
2. Research Grants:				
a. Non-competing terminated in 1976	--	72,921,000	--	-29,760,000
3. Fellowships				
a. Phase out of post doctoral research fellowship awards	--	416,000	--	-181,000
4. Training Grants:				
a. Phase out of graduate training grants	--	3,800,000	--	-3,800,000
Subtotal	--	--	-32	-33,774,000
Total, decreases	--	--	-32	-33,818,000
Total, net change	--	--	-32	+1,825,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
195	Communicative Disorders.....	$ 16,797,000	$ 18,056,000	$ 17,067,000	-$989,000
196	Neurological Disorders.....	57,814,000	64,392,000	63,976,000	-416,000
201	Stroke and Nervous System Trauma.....	14,892,000	16,007,000	15,902,000	-105,000
204	Fundamental Neuro-sciences.....	13,552,000	14,924,000	15,057,000	+133,000
206	Intramural Research and Direct Operations	31,791,000	30,782,000	33,897,000	+3,115,000
	Positions	505	537	505	-32
209	Program Management...	293,000	285,000	295,000	+10,000
	Positions	6	6	6	--
	Standard Level User Charge.....	261,000	261,000	338,000	+77,000
	Total obligations	135,400,000	144,707,000	146,532,000	+1,825,000
	Total positions	511	543	511	-32

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	543	511	-32
Full-time equivalent of all other positions	55	55	--
Average number of all employees	564	561	-3
Personnel compensation:			
Permanent positions	$10,050,000	$10,370,000	+$320,000
Positions other than permanent	1,523,000	1,571,000	+48,000
Other personnel compensation	238,000	243,000	+5,000
Subtotal, personnel compensation	11,811,000	12,184,000	+373,000
Personnel benefits	1,445,000	1,479,000	+34,000
Travel and transportation of persons	511,000	411,000	-100,000
Transportation of things	75,000	85,000	+10,000
Rent, communications and utilities	620,000	681,000	+61,000
Printing and reproduction	200,000	210,000	+10,000
Other services	2,832,000	3,977,000	+1,145,000
Project contracts	10,835,000	11,191,000	+356,000
Payment to NIH Management Fund	8,525,000	9,542,000	+1,017,000
Supplies and materials	2,115,000	2,463,000	+348,000
Equipment	3,194,000	3,498,000	+304,000
Grants, subsidies and contributions	102,544,000	100,811,000	-1,733 000
Total obligations by object	144,707,000	146,532,000	+1,825,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1976 House Report	
1. The Committee expects NINCDS to use a portion of the increased funds provided in this bill to expand its research efforts on diabetes and to coordinate its diabetes research program with the other NIH Institutues in accordance with the National Diabetes Mellitus Research and Education Act.	1. The Institute has made an intensive analysis of its programs to determine the amount of research being conducted on diabetes. This information has been submitted for inclusion in an overall NIH report.
1976 Senate Report	
1. The Committee's interest in the area of autistic research remains strong. The Committee has not been notified of any NINCDS efforts in this important area, and directs that a report be given the Committee relating to this.	1. The NINCDS is sponsoring a workshop in February, 1976 on the Neurobiological Basis of Autism. The major goals of this workshop are: a) to provide a working definition of autism, which would serve as a common basis for neurobiological research; b) to provide assessments of the current status of neurobiological research on autism; and c) to identify promising research areas and provide recommendations regarding appropriate research activities that would advance scientific knowledge regarding the neurobiological basis of autism.
2. During the past year two new drugs for the treatment of epilepsy were released on the basis of clinical data from Institute studies. It is expected that another new anti-epileptic drug will be ready for clinical release next year. The Committee encourages further work and the dissemination of information in this important area.	2. The Institute will continue its support and collaboration in clinical research of investigational new antiepileptic drugs in the search for agents providing greater seizure control and fewer side effects. The Institute has established comprehensive research and treatment programs for epilepsy and related convulsive disorders. The Commission for the Control of Epilepsy and its Consequences, mandated by the Congress in 1975, will begin deliberations in 1976 and report its findings and recommendations to the Secretary of HEW and to the Congress.

Authorizing Legislation

Legislation	1977 Authorization	1977 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	$141,191,000 2/
Public Law 90-639, Sec. 7--National Institute of Neurological Diseases and Stroke.....	Indefinite	
Title IV, Part I--National Research Service Awards.....	1/	$ 5,341,000 2/

1/ Authorization expired June 30, 1975; extension legislation is pending.

2/ Funding estimate only.

National Institute of Neurological and Communicative Disorders and Stroke

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	115,216,000	136,807,000 5/	136,807,000 5/	
Items not considered (---)		(7,900,000)	(7,900,000)	
1977	146,532,000			

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 as authorized by PL 93-192.
4/ Excludes contracts not considered by House due to lacking authorization.
5/ Excludes training programs not considered by the House, Senate or the Conferees due to lacking authorization.

Note: The figures presented in this table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsiblity for funding of general research support grants is no longer the function of this institute in 1977. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes.

National Institute of Neurological and Communicative Disorders and Stroke

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1967	$106,418,000	$111,296,000	$116,296,000	$116,296,000
1968	128,633,000	128,633,000	135,633,000	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	130,672,000	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	136,546,000 5/	136,546,000 5/	
Items not considered	(---)	(7,900,000	(7,900,000)	
1977	146,532,000			

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 as authorized by PL 93-192.
4/ Excludes contracts not considered by House due to lacking authorization.
5/ Excludes training programs not considered by the House, Senate, or the Conferees due to lacking authorization.

Justification

Program	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
1. Communicative Disorders.....	$ 16,797,000	$ 18,056,000	$ 17,067,000	-$989,000
2. Neurological Disorders.....	57,814,000	64,392,000	63,976,000	-416,000
3. Stroke and Nervous System Trauma.....	14,892,000	16,007,000	15,902,000	-105,000
4. Fundamental Neuro-sciences.....	13,552,000	14,924,000	15,057,000	+133,000
5. Intramural Research and Direct Operations	31,791,000	30,782,000	33,897,000	+3,115,000
Positions	505	537	505	-32
6. Program Management...	293,000	285,000	295,000	+10,000
Positions	6	6	6	--
7. Standard Level User Charge.....	261,000	261,000	338,000	+77,000
Total obligations	135,400,000	144,707,000	146,532,000	+1,825,000
Total positions	511	543	511	-32

General Statement

Research funded by the National Institute of Neurological and Communicative Disorders and Stroke is intended to increase understanding of the structure and function of the brain, the spinal cord, and the related nervous and sensory systems; and to combat the many disorders which afflict these organs. Many of these disorders such as cerebray palsy, multiple sclerosis, muscular dystrophy and Parkinson's disease, interfere with physical mobility and cause long-term disability. Others interfere with education and employment; such as epilepsy, deafness, and speech disorders. Stroke is the third leading cause of death in this country; and head and spinal cord trauma are major causes of serious and permanent disability.

NINCDS has organized its efforts in four carefully focused programs which support and conduct research programs directed to these health problems and scientific challenges. In addition to the problem-oriented extramural research programs which support research by grant and conduct research by contract, the Institute's intramural research program conducts a broad range of basic and clinical investigations based at the National Institutes of Health in Bethesda. This overall program represents a balanced, and coordinated, attack on these health and scientific problems. These programs address themselves to the following specific problems:

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; and

Communicative disorders including disorders of hearing and equilibrium, speech and language, and other higher brain functions, and disorders of other senses.

Further description of the four extramural research programs and the intramural research programs follow.

Communicative Disorders Program

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Communicative Disorders...	$16,797,000	$18,056,000	$17,067,000	-$989,000
Subactivities:				
Hearing and equilibrium	12,229,000	12,938,000	12,658,000	-280,000
Speech and language....	2,957,000	3,235,000	3,082,000	-153,000
Research career programs.....	158,000	205,000	277,000	+72,000
Research training programs.....	1,453,000	1,678,000	1,050,000	-628,000
Total.....	16,797,000	18,056,000	17,067,000	-989,000
Budget Mechanism:				
Research Grants				
Regular.....	13,761,000	14,587,000	13,807,000	-780,000
Special.....	308,000	355,000	727,000	+372,000
Subtotal.....	14,069,000	14,942,000	14,534,000	-408,000
Fellowships.....	700,000	811,000	1,050,000	+239,000
Training grants.....	753,000	867,000	---	-867,000
Research and development contracts.....	1,275,000	1,436,000	1,483,000	+47,000
Total.....	16,797,000	18,056,000	17,067,000	-989,000

The Communicative Disorders Program of NINCDS 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. The disorders of human communication are some of the most frequent disabilities in our society, for approximately 10 percent of the population, or over 20 million individuals, are so affected. Of these disorders, hearing loss is the most prevalent. The most recent census of the deaf indicates between 13 and 14 million with sufficient hearing loss to significantly affect their ability to function effectively in everyday activities. Since such a defect is not visible and usually is not a cause of death, the problem is often downgraded. However, one cannot overlook the economic factors of: Cost for special education and rehabilitation; and loss of potential earning power for self-support. Even more important for the individual and the family involved is the change in the quality of life caused by such disabilities.

The communication process may be impaired by a multitude of problems including poor amplification of the message, 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, and from more generalized neurological disorders causing impaired muscle coordination.

In each of these areas where the potential for a break in the communicative process is present, significant gaps in our knowledge still exists.

Individual research grants, program projects, and clinical research centers are all being utilized by the NINCDS to study in depth the basis of human communication and its disorders. The primary emphasis is on prevention, but where disorders of function already exist the emphasis is on improvements in diagnosis and treatment. The Laboratory of Neuro-Otolaryngology on the Bethesda campus is providing leadership in revealing some of the inner ear functions which were previously not understood. Chief among these is the process of transduction, whereby sound waves (mechanical energy) entering the ear are converted into nerve impulses (electrical signals) for transmission to the brain for processing, utilization, and storage. Understanding of this mechanism is the key to the development of rational methods of dealing with the most prevalent type of hearing loss and the type which up to now has not been amenable to treatment, i.e., sensori-neural hearing loss.

The NINCDS has indicated a special interest in three problems of human communication. One of these is replacing lost hearing by stimulating the nerve endings of the inner ear through the so-called cochlear implant. Workshops devoted to this subject which were sponsored by the Institute recommended a number of projects which should be carried out in this area. A majority of these recommendations have been undertaken and are ongoing such as: The development and miniaturization of suitable electrodes; the evaluation of long-term effects of stimulation on nerve tissue, and the objective evaluation of patients who have already received an implant device. The Institute is anticipating funding a limited number of auditory implant centers where such work can be continued.

The second problem is serous (secretory) otitis media, a very prevalent middle ear affliction in young children, which is a major cause of hearing loss. The NINCDS is helping to make available the results of the recent International Workshop on this subject where many of the grantees of the Institute presented the results of their ongoing studies. The results of this Workshop have already produced new leads for research on this baffling and disabling condition.

The third problem is the control of agents which cause damage to the functioning of the ear. Knowledge in this area should provide better protection of the ear from such agents. Common examples of such agents include noise and drugs which are sometimes required for therapeutic use.

In addition, directed research through the contract program encompasses several projects which include development of a measure of everyday communication skills in aphasic (language impaired) adults; evaluation of newly developed speech tests to determine the potential of hearing aid use; evaluation of a wearable master hearing aid for possible utilization to improve hearing aid fitting; evaluation of a newly developed sensory aid for the profoundly deaf to facilitate their lipreading ability; and development of methods for screening for language and speech problems in preschool children.

Neurological Disorders Program

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Neurological Disorders....	$57,814,000	$64,392,000	$63,976,000	-$416,000
Subactivities:				
Neurological disorders of early life.....	10,539,000	11,649,000	11,848,000	+199,000
Neurological disorders of adult life.....	4,995,000	5,534,000	5,553,000	+19,000
Epilepsy.....	7,215,000	8,008,000	8,524,000	+516,000
Sclerosing disorders.....	5,217,000	5,780,000	5,794,000	+14,000
Neuromuscular disorders..	6,815,000	7,549,000	7,566,000	+17,000
Infectious diseases of the central nervous system.....	2,933,000	3,256,000	3,318,000	+62,000
Tumors of the nervous system.....	837,000	929,000	938,000	+9,000
Neuroendocrine studies...	3,822,000	4,235,000	4,240,000	+5,000
Learning and behavior....	2,361,000	2,615,000	2,619,000	+4,000
Other sensory disorders..	7,180,000	7,954,000	7,969,000	+15,000
Research career programs.....	1,163,000	1,507,000	1,608,000	+101,000
Research training programs.....	4,737,000	5,376,000	3,999,000	-1,377,000
Total.....	57,814,000	64,392,000	63,976,000	-416,000
Budget Mechanism:				
Research Grants				
Regular.....	42,184,000	46,859,000	46,115,000	-744,000
Special.....	4,032,000	4,526,000	5,980,000	+1,454,000
Subtotal.....	46,216,000	51,385,000	52,095,000	+710,000
Fellowships.....	2,663,000	2,988,000	3,999,000	+1,011,000
Training grants.....	2,074,000	2,388,000	---	-2,388,000
Research and development contracts.....	6,861,000	7,631,000	7,882,000	+251,000
Total.....	57,814,000	64,392,000	63,976,000	-416,000

Neurological Developmental Disorders of Early Life. NINCDS will support research on the neurological basis of developmental disorders of children including the areas of cerebral palsy, autism, mental retardation, learning and behavior disorders, central nervous system birth defects, heritable muscle and neurological diseases, and minimal brain dysfunction. In addition, the Institute will continue and complete the comprehensive analysis and interpretation of Collaborative Perinatal Project data, provide for the archival and retrieval

system of the Collaborative Perinatal Project data and will promote and support appropriate research use of this national data resource commensurate with its goals and mission.

The Institute is sponsoring a workshop in February, 1976 on the Neurobiological Basis of Autism. The major goals of this workshop are: 1) to provide a working definition of autism, which would serve as a common basis for neurobiological research; 2) to provide assessments of the current status of neurobiological research on autism; and 3) to identify promising research areas and provide recommendations regarding appropriate research activities that would advance scientific knowledge regarding the neurobiological basis of autism. In 1977, an appropriate research program on autism will be initiated.

The data collection phase of the Collaborative Perinatal Project has been completed. The analysis and interpretation of the data on the children up to age seven and eight years will be completed in 1977 and will include ten primary areas: cerebral palsy and motor disorders; mental retardation, vision abnormalities; convulsive disorders; learning disorders; 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. The analysis of these data has identified groups of children with special interest and these subgroups of children will receive extended follow-up and study. The subgroups are children with febrile seizures, and convulsive disorders, cerebral palsy, learning and behavior disorders and communicative disorders. A controlled study of children with febrile seizures will evaluate whether preventive therapy will reduce the number of children who subsequently develop epilepsy or other disabilities.

Epilepsy. The Commission for the Control of Epilepsy and its Consequences, mandated by the Congress in 1975, will begin deliberations in 1976 and report its findings and recommendations to the Secretary of Health, Education, and Welfare and to the Congress. The Comprehensive National Plan for the Control of Epilepsy and its Consequences will contain specific recommendations for expanded research, treatment, socioeconomic and rehabilitation efforts. The Institute will continue its support and collaboration in clinical research of investigational new antiepileptic drugs in the search for agents providing greater seizure control and fewer side effects. The Institute has established comprehensive research and treatment programs for epilepsy and related convulsive disorders. These programs stress a comprehensive approach to applied and fundamental research and are strongly oriented toward the development of new and improved methods of diagnosis and treatment and rehabilitation regardless of age or severity. Primary emphasis is on the application of new research findings to patients. The ultimate goal of these programs is the development of new antiepileptic drugs in the search for complete control of seizures the reduction of the debilitating side effects of presently available drugs, and the restoration of the patients with controlled seizures to a useful and productive life.

Multiple Sclerosis and Other Demyelinating Diseases. In multiple sclerosis, NINCDS has welcomed the completion of work of the National Advisory Commission on Multiple Sclerosis. The recommendations in the Commission's report submitted to the Secretary of HEW and to the Congress have been supported 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 four additional research centers making a total of seven. In an attempt to discover the cause of this disease, the Institute is conducting and supporting approximately 50 research projects. One-half of these projects are in biochemistry and neurochemistry; the other half relates to immunology,

neurophysiology, pathology, virology and clinical studies. Chemical and metabolic characteristics of normal and abnormal myelin have been investigated extensively 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. As part of this phase of the program, the Neuroimmunology Branch of the Intramural Research program has been established. Five NINCDS-supported multidisciplinary clinical programs are conducting studies on patients, involving immunological, virological, and neurochemical aspects relevant to demyelinating disease. A national survey of incidence, prevalence and cost of multiple sclerosis is ongoing and the epidemiological survey of the high-incidence Shetland and Orkney Islands will be completed this coming year.

Muscular Dystrophy, Myasthenia Gravis, and Other Neuromuscular Diseases. Research in this group of diseases is centered in about 125 research projects in numerous hospitals, medical schools, and universities, including three program project grants, and in the Medical Neurology Branch of the Institute's Intramural Research 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 NINCDS scientists of freeze-fracture electron microscopy to obtain a panoramic, birds-eye-view of cell membrance 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 NINCDS scientists that permits the study of active muscles, in contrast to previous conventional techniques what are suitable only for muscles at rest.

Infectious Diseases of the Central Nervous System. In addition to the Institute's program in slow and atypical viruses described below in the section on the Intramural Research Program, the Institute has a highly significant program carried on by its grantees and contractors, and by the Intramural Research Program in relation to the Collaborative Perinatal 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.

Degenerative Disorders. Research under this category includes work related to Parkinsonism, Huntington's Disease and other involuntary movements and hyperkineses, and general extrapyramidal studies. Although L-DOPA produces remarkable improvement in most Parkinsonism patients at times it has unpleasant side effects and some patients do not respond to it at all. Approximately 27 research grants are concerned with improving the efficacy of L-DOPA, exploring other treatments, and examining hypotheses that deal with the etiology of Parkinson's Disease.

Eight research grants are concerned with early diagnosis and treatment of Huntington's Disease. Although physostigmine has been demonstrated to be effective in treating the involuntary movements associated with this disease, other agents are being examined.

Certain studies focus on Alzheimer's Dementia utilizing clinical, biochemical, light microscopic ultrastructural, and other experimental approaches. Related work is concerned with the determination of a defect in axonal or dendritic flow of particulate matter in cortical neurons of patients suffering from dementia. Other studies emphasize the development of experimental models for the analysis of the immunobiology of age-dependent CNS disease. About 22 research grants support activities in this area.

Five research centers have been established to focus efforts on studies of degenerative disorders.

Neoplasms (Tumors) of the Brain and Nervous System. Tumors of the brain and nervous system constitute an important health problem for children and the aged. Nearly one-half of all those who die each year of neurological disorders other than stroke succomb to brain tumors. Because of the special characteristics of nervous system tissue, these neoplasms do not respond to therapies found useful on tumors in other organs. Also, there is preliminary but substantial evidence that the nervous system is an important reservoir of viruses suspected of being tumor causing (oncogenic). In collaboration with the National Cancer Institute, the Institute is continuing to explore these leads on the unique problem of tumors of brain and other nervous tissue.

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Stroke and Nervous System Trauma Program

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Stroke and Nervous System Trauma.....	$14,892,000	$16,007,000	$15,902,000	-$105,000
Subactivities:				
Stroke.....	7,981,000	8,478,000	8,670,000	+192,000
Trauma and Injury.....	6,557,000	6,969,000	6,937,000	-32,000
Research career programs.....	130,000	168,000	157,000	-11,000
Research training programs.....	224,000	392,000	138,000	-254,000
Total.....	14,892,000	16,007,000	15,902,000	-105,000
Budget Mechanism:				
Research Grants				
Regular.....	9,740,000	10,385,000	9,873,000	-512,000
Special.....	4,024,000	4,212,000	4,839,000	+627,000
Subtotal.....	13,764,000	14,597,000	14,712,000	+115,000
Fellowships.....	---	134,000	138,000	+4,000
Training grants.....	224,000	258,000	---	-258,000
Research and development contracts.....	904,000	1,018,000	1,052,000	+34,000
Total.....	14,892,000	16,007,000	15,902,000	-105,000

Within this program, there are six major scientific program efforts: Stroke, Head Injury, Spinal Cord Injury, Nervous System Regeneration, and Chiropractic and Manipulative Therapy.

Stroke, the third leading cause of death in the United States, has an annual mortality rate of over 200,000. Moreover, each year an additional 300,000 persons who survive strokes suffer permanent physical and mental disabilities. The Institute is continuing to give the highest priority to a coordinated research program in this area by means of investigator-initiated research, research and development contracts, and stroke clinical research centers (fifteen of which are now active). In addition, a pilot program of comprehensive stroke centers has been planned for initiation this year. This program will emphasize the evaluation and dissemination of laboratory and university clinical findings in community settings, with special attention to correlation of the initial or acute stage management procedures with the subsequent rehabilitation outcome. A recent development of particular promise in monitoring the acute phase of a stroke is the technique of computerized axial tomography (CAT), a non-invasive x-ray scanning instrument combined with a computer. These scanners are now in operation at NINCDS Clinical Research Centers and are being both evaluated as diagnostic and monitoring

techniques and further developed to provide more precise information for the diagnosis of an impending stroke. Examples of other areas of interest in the Institute's stroke research program include new methods of therapy being developed to protect a patient's brain at the beginning of a stroke or during its acute phases and studies of the role of the hypothalamus as a primary cause of essential hypertension (high blood pressure).

Head Injury. Head Injury is one of the most common causes of death due to trauma (e.g., traffic accidents, industrial accidents, sports). 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 are the several approaches being fostered in the Institute's head injury research program. One major problem confronting the physician is the evaluation of coma following injury to the brain. In order to resolve this dilemma, a national cooperative study has been launched to provide the means of differentiating between head injured patients who have incurred irreversible damage at the time of the injury and those who are comatose as a result of reversible complications of the injury. To parallel this, improved therapeutic methods of dealing with brain swelling, the most common cause of coma following head injury, are being developed. Through its clinical research center activity, five regional head injury clinical research centers are serving as focal points for the coordination, evaluation and dissemination of laboratory and clinical data in this research area.

Spinal Cord Injury. Spinal cord injury as a result of traffic and recreational accidents continues to be a serious problem to the victim, his family, and the community. In light of this, the Institute has focused special attention on the problem of preventing permanent damage to the injured spinal cord and at the least, preventing the cord's self-destruction. Preliminary data indicate that if the acutely injured cord is treated immediately and adequately, permanent damage may be minimized or prevented; however, more information is needed in regard to improved methods for identifying the specific site and extent of injury and to new approaches to both specific and general therapy of the injured person. The applicability of CAT scanning to these problems will be evaluated. In addition, there is need to exploit further existing opportunities at the regional spinal cord injury clinical research centers to demonstrate how best to translate the newest scientific information into better methods of clinical therapy. The Institute currently supports five spinal cord injury clinical research centers.

Central Nervous System Regeneration. Paralleling these research efforts on Stroke, Head Injury and Spinal Cord Injury is the Institute's targeted program on central nervous system regeneration. If the function of destroyed segments of the brain and spinal cord could be restored, then many of the millions of now permanently disabled citizens could enjoy at least a partial return of function. The solution of this problem is surely one of the most complex in the entire field of the biomedical sciences and will demand focused attention for several years before its solution is achieved. To help identify and focus needed research efforts in this area, the Institute's National Advisory Council has recently released a comprehensive report on "Growth and Regeneration in the Central Nervous System" This report has been widely distributed and will serve as a basis for stimulating increased research efforts in this important area.

Chiropractic Research; Research on Manipulative Therapy. At the direction of the Congress, the pilot phase of a coordinated national effort on research on chiropractic and manipulative therapy has been completed. A series of research workshops identifying the state of the art in these research areas has been completed and the proceedings of these symposia are in press. A modest

number of pilot research programs have already been initiated, focused particularly on the biomechanics and neurophysiology of subluxation and altered vertebral mechanics. Also, explorations are in progress to design clinical trials of x-ray and palpatory diagnostic methods and of manipulative therapy for low back pain. In addition, a modest program of research training has been identified which will provide manipulative clinicians (chiropractors, osteopaths and medical physicians) with the opportunity of increasing their research skills for application to these problems.

Fundamental Neurosciences Program

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Fundamental Neurosciences	$13,552,000	$14,924,000	$15,057,000	+$133,000
Subactivities:				
Nervous System Studies related to normal function	7,198,000	7,860,000	8,081,000	+221,000
Multicategorical	5,671,000	6,213,000	6,419,000	+206,000
Research career programs	306,000	397,000	403,000	+6,000
Research training programs	377,000	454,000	154,000	-300,000
Total	13,552,000	14,924,000	15,057,000	+133,000
Budget Mechanism:				
Research Grants				
Regular	11,853,000	12,973,000	13,426,000	+453,000
Special	656,000	747,000	703,000	-44,000
Subtotal	12,509,000	13,720,000	14,129,000	+409,000
Fellowships	128,000	167,000	154,000	-13,000
Training grants	249,000	287,000	---	-287,000
Research and development contracts	666,000	750,000	774,000	+24,000
Total	13,552,000	14,924,000	15,057,000	+133,000

All biomedical research may ultimately lead to solutions of health problems. However, it is the firm belief of the vast majority of biomedical scientists that the more fundamental the questions toward which research is directed, the greater will be the return in ultimately applicable results. Because the basic understanding of how the brain and nervous system develops, works, and is structured is essential to a successful attack upon the varied neurologic and sensory disorders, NINCDS continues to support and conduct basic research in the fundamental neurosciences.

In the wide range of research grant and contract proposals from which the NINCDS selects its programs, some are more directly applicable to specific research than others. These are assigned to the disease categorical programs, Neurological Disorders, Communicative Disorders, and Stroke and Trauma. Other research proposals are directed at more fundamental questions about the basic structure and function of the nervous system, its chemistry, the action of drugs on it, and on the individual nerve cells with their tiny terminal processes by which they communicate with one another. The answers to such fundamental questions about the normal nervous system are required in order to understand the even more complex processes of disease. It is the basic neuroresearch efforts such as these, which constitute the Fundamental Neurosciences Program.

Even within this program there is wide variability in the lead time required before research findings can be applied to treatment of disease. For example there is increased effort in application of computers to neurobiological problems of pattern recognition in studying how groups of nerve cells work together to control muscle movement, problems of computer assisted analysis of brain waves (EEG). Sleep is classified into different types and the normal and abnormal balance between these different types can be studied with the help of computers. Basic mechanisms in sensory neurophysiology must be understood in order to learn how to preprocess sound so that electrical stimulation of the nervous system of deaf individuals can be utilized for congenital speech communication.

Some of the most fundamental studies in this program relate to the manner in which interconnections between nerve cells affect the function of the nervous system. The nervous sytem is not "hard-wired" like a telephone switchboard, rather, it is thought, the synapses or connections at nerve endings continue to change with time, new ones forming and old ones dissolving. Such changes in "connectivity" are stimulated by changes in usuage or activity of nerve pathways. Increased efforts are planned for these studies of the functional modification of the nervous system with usuage.

Contract studies continue to explore the mechanisms by which electrical stimulation of the nervous system can be used to induce useful patterns of nerve cell activity. Other studies emphasize the damage which such electrical nerve stimulation may produce and search for techniques to maximize the safety factor between effective stimulation and lasting irreversible damage. Implanted electronic devices can be used to stimulate the spinal cord and its nerve roots in such a way that urinary bladder evacuation occurs. Failure of the bladder to drain properly is one of the major causes of urinary infection and death in paraplegic patients. Thus, in this area fundamental studies of the normal bladder reflex mechanism and the development of successful techniques for nervous system stimulation by remote control may lead very directly to relief of human disease.

New research projects capable of solving such basic questions about the nervous sytem require the training and development of highly skilled scientists over many years. These teams cannot be "turned on and off" from year to year. An opportunity to try out new research ideas is as important as the continued support over the years required to realize long range research goals. Constraints during FY 76 have seriously interfered with the development of new initiatives, particularly in the Fundamental Neurosciences Program. It will be a part of the policy of the FNP in FY 77 to support and encourage reformation of the best of these new initiatives. In the contract area, a directed research program will continue to explore the feasibility of new types of neural prostheses (nerve substitutes) and fundamental techniques of bioengineering.

Annual Workshops are held to facilitate the exchange of new information between FNP staff, acting as an information hub, and grantee principal investigators and contractors.

Intramural Research and Direct Operations

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Laboratory and Clinical Research.....	$20,784,000	$18,937,000	$21,701,000	+$2,764,000
Positions	273	290	273	-17
Research Management and Program Services.....	11,007,000	11,845,000	12,196,000	+351,000
Positions	232	247	232	-15
Standard Level User Charge	261,000	261,000	338,000	+77,000
Total obligations...	32,052,000	31,043,000	34,235,000	+3,192,000
Total positions	505	537	505	-32

The Intramural Research Program of NINCDS conducts research related to the nervous system and its disorders in laboratories and clinics in Bethesda, Maryland. Over 180 research projects are currently active: Approximately 57% of Intramural resources are devoted to fundamental research and 43% to clinically applied studies. In the basic research areas, major budgetary support currently is devoted to neurophysiologic (15%) and biochemical approaches (8%) to the understanding of brain function as well as to the basic mechanisms by which viruses and other infectious agents modify the structure and activity of nervous system tissues (13%). In the clinical research areas, demyelinating conditions (9.3%), infectious diseases (6.3%), and congential disorders (5.1%) of the nervous system presently command the largest research allocations. Some of the most promising research areas to be pursued during the next fiscal year are summarized in the following sections.

Clinical Research Programs. The Institute's clinical programs conduct research on a variety of neurological and communicative disorders arising as a result of maldevelopment or malfunction of the nervous system. Emphasis continues to be placed on the rapid application of new knowledge developed from basic research, to the development of improved preventive, diagnostic, and therapeutic measures for nervous system disease.

In the medical neurology area, studies will continue on the causes and treatments of motor neuron disease, myopathies, dystrophies, and diseases of the neuromuscular junction. Increased emphasis will be placed on immunological aspects of certain of these disorders especially myasthenia gravis. In addition, a major new effort has been undertaken to evaluate the possible role of viral agents in the pathogenesis of a number of central nervous system disorders, including multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease and Parkinson's disease.

In the developmental and metabolic neurology areas, research continues to be directed towards the development of improved diagnostic and therapeutic techniques for such inherited disorders of lipid metabolism as Fabry's, Tay-Sachs, Gaucher's, and Niemann-Pick disease. Each of these disorders arises as a result of a genetically determined defect in a single enzyme. Efforts to perfect biochemical tests for the antenatal diagnosis of these and related conditions as well as to expand clinical trials of enzyme replacement therapy will be strongly supported.

In the surgical neurology area, research is focused on therapeutic programs in focal epilepsies, head injury, cerebral tumors, and certain dyskinesias. In this group, special attention will be directed towards the development of experimental stroke models, clinical trials of improved chemotherapeutic and immuno-

suppressive therapies for central nervous system tumors, and to the preclinical and clinical testing of microsurgical therapeutic approaches to cerebrovascular insufficiency.

The communicative disorders area has also witnessed an expansion of clinical research. Recently initiated studies of speech production disorders in patients with Parkinson's disease using speech science instrumentation should provide objective measures of speech dysfunction applicable to patients with a variety of neurologic disorders.

Laboratory Research Programs. The Institute's research laboratories conduct a broad array of projects devoted to creating the knowledge used to establish a base for developmental and applied work. The projects are investigator-initiated and are carried on with the laboratories by individual scientists or groups, depending on the type of activity necessary. The recognition that progress depends on the creativity and ingenuity of an individual who makes important discoveries of broad applicability to medicine justifies support for investigator-initiated research. The most efficient way to generate discoveries important to prevention or treatment of disease is to encourage creative individuals or small groups who pursue ideas arising from their own knowledge and expertise. Although not often highly visible in the final application of the discovery, the investigator-initiated research effort is the predominate if not the only mechanism to create the new knowledge with which to achieve progress.

A strong thrust to gain new knowledge about the function of nerve cells and the networks they form will continue. The basic mechanisms of how nerve cells transfer information between cells remains poorly understood. Also inadequate is our knowledge of the metabolic and chemical environment which allows nerve cells to exist for scores of years and stay alive and functioning. Much more information is needed about the electrical activity of individual nerve cells and the chemicals released when the cells become active. It is especially necessary to define which chemicals are released and to determine the location of their activating or inhibiting effects on other cells. Also needed is extensive studies on the storage and release of brain cell chemicals and how to activate or block that storage or release by the use of drugs or other means. Biochemical, microspectrophotometric, neurophysiological and cytological studies on invertebrates and vertebrates, electrical recording from single cells, electronmicroscopy especially with scanning and 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 and ionic or molecular transport.

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 and between 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 and synthesis of complex lipids, myelination of the nervous system, genetic regulation in human cells and regulation of viral nucleic acids among many others.

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 as it relates to stroke, 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. The neural mechanisms of learning and behavior are investigated in lower animal forms where simpler nervous systems increase the probability of progress.

Also emphasized are studies on motor control systems in the spinal cord or cerebral cortex, and techniques for obtaining information transfer within the nervous system. An effort to study the biologic mechanisms of hearing continues. 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 multiple sclerosis or amyotrophic lateral 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 research in immunology related to viruses will necessarily be expanded. Elucidation of the mechanisms of interference between viruses and defective virus particles continue. These studies examine the possibility that harmless defective particles of viruses may be effective in preventing or treating viral infections.

This activity also includes support for the offices of program planning and evaluation, biometry and epidemiology, administrative management functions and for the administration of the Institute's grants and contracts as they relate to the four major program areas. This staff will continue to manage the varied extramural programs described above. In addition, special efforts will be made to facilitate the most careful and sound scientific judgments by the Institute Director and his staff by improving available management and scientific information and continued efforts to combine the scientific management of grant and contracts research.

Program Management

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Program Management.....	$293,000	$285,000	$295,000	+$10,000
Positions	6	6	6	--

The recent reorganization of the Institute established four major research programs; communicative disorders, neurological disorders, stroke and nervous system trauma, and fundamental neurosciences. This budget program reflects those members of the Institute who are responsible for the program management and direction of research in the neurological and sensory disorders. They include the Institute Director, the Deputy Director, and the directors of the four major programs mentioned above.

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]

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$18,056,000	Indefinite	--	$17,067,000

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, 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 1976: In 1976, under this program 179 research grants, 40 fellowships, 13 training grants, and 12 contracts were awarded. The Institute's programs in 1976 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 1977: The estimate for 1977 provides for 167 research grants, 47 fellowships, 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 the Intramural Research Program.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$64,392,000	Indefinite	--	$63,976,000

Purpose: Of the four major research program segments, the Neurological Disorders Program 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 1976: In 1976, 836 research grants, 169 fellowships, 31 training grants, and 43 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 1977: The estimate for 1977 provides for 809 research grants, 249 fellowships, and 45 contracts. Research emphasis in 1976 will be focused on: epilepsy including the establishment of one of 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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$16,007,000	Indefinite	--	$15,902,000

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 1976: In 1976, support was provided for 138 research grants, 10 fellowships, 14 training grants, and 8 contracts. Research was directed towards stroke, head injury, spinal cord injury, and nerve growth and regeneration.

Objectives for 1977: The estimate for 1977 provides for 143 research grants, 10 fellowships, and 9 contracts. Research programs on stroke during 1977 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.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$14,924,000	Indefinite	--	$15,057,000

Purpose: Support of research in those areas of the fundamental neurosciences not identifiable with the other three NINCDS 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 researeh 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 1976: In 1976, 192 research grants, 12 fellowships, 4 training grants, and 3 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 1977: The estimate for 1977 provides for 194 research grants, 11 fellowships, 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.
its diseases.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

Program Purpose and Accomplishments

Activity: Intramural Research and Direct Operations (Public Health Service Act, Public Law 410, Title IV, Part D)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
537	$31,043,000	Indefinite	505	$34,235,000

Purpose: The intramural research activities of the Institute comprise a broad program of investigation of the basic characteristics of the nervous system and its diseases.

Explanation: Supporting the intramural 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.

This program also includes support for the offices of program planning and evaluation, biometry and epidemiology, administrative management functions and for the administration of the Institute's grants and contracts as they relate to the four major program areas.

Accomplishments in 1976: Several promising new therapies were developed for treatment of epilepsy, and understanding the burst of abnormal electrical activity of brain cells during the epileptic seizure. In the Laboratory Research area, advancement in knowledge has been obtained of the structure of the nervous system and interpreting basic abnormal changes, the blood-brain barrier and its functions, and the chemical organization of the brain and nerves.

Objectives for 1977: In 1977 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 Purposes and Accomplishments

Activity: Program Management (Public Health Service Act, Public Law 410, Title IV, Part D)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
6	$285,000	Indefinite	6	$295,000

Purpose: This activity provides the program direction of the Institute's research programs and activities.

Explanation: Included in this program is the Institute Director, the Deputy Director, and the four Directors of each of the Institute's major programs.

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Estimate	Transition Quarter
1. Communicative Disorders	$18,056,000	$3,978,000
2. Neurological Disorders	64,392,000	14,178,000
3. Stroke and Nervous System Trauma	16,007,000	3,804,000
4. Fundamental Neurosciences	14,924,000	3,507,000
5. Intramural Research and Direct Operations	31,043,000	7,423,000
6. Program Management	285,000	74,000
Total	144,707,000	32,964,000

Explanation

The estimate for the three-month transition quarter reflects a continuation of the programs of the NINCDS. Estimates for individual programs and mechanisms were based on historical accounting data for the first quarter of FY 1976, modified to include built-in increases. Funds will provide for the same level of non-competing and competing continuation research grants with no new grants being awarded. Fellowship funds will allow the award of all non-competing with no new fellowships initiated.

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THURSDAY, FEBRUARY 26, 1976.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. RICHARD M. KRAUSE, DIRECTOR
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. JOHN R. SEAL, ACTING DEPUTY 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
ROBERT C. PATRICK, BUDGET OFFICER, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

OPENING STATEMENT

Mr. NATCHER. Dr. Krause, we are pleased to have you before the committee at this time. I have examined your statement. You have an excellent statement to present to the committee. Unless there is some objection on your part, we would like to insert your statement in the record as if you had read it.

We are running just a little behind and we would like to get directly to the questions. We will also insert in the record at this point your biographical sketch.

[The material follows:]

BIOGRAPHICAL SKETCH

Name: Richard M. Krause, M.D.

Position: Director, National Institute of Allergy and Infectious Diseases.

Birthplace and date: Marietta, Ohio, January 4, 1925.

Education: A.B., Marietta College, 1947. M.D., Case Western University School of Medicine, 1952.

Experience: Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1975 to present. Professor, Rockefeller Universtiy, and senior physician to the Hospital, 1968–75. Associate professor, Rockefeller University, and physician to the hospital, 1966–68. Professor of epidemiology and professor of medicine, Washington University School of Medicine, St. Louis, 1965–66. Professor of epidemiology and associate professor of medicine, Washington University School of Medicine, 1962–65. Associate professor, Rockefeller Institute, and physician to the hospital, 1961–62. Assistant professor, Rockefeller Institute, and associate physician to the Hospital, 1957–61. Assistant, Rockefeller Institute, and assistant physician to the hospital, 1954–57. Internship and residency training, internal medicine, Barnes Hospital, 1952–54. Research Fellow, Department of Preventive Medicine, Case Western University School of Medicine, 1950–51.

Association memberships: Association of American Physicians. American Society for Clinical Investigation. American Society for Microbiology. The Harvey Society. Central Society for Clinical Research. Sigma Xi. American Association for the Advancement of Science. American Venereal Diseases Association. Infectious Diseases Society of America. Royal Society of Medicine. Practitioner's Society of New York.

Member, Infectious Disease Advisory Committee, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1970–74. Board of Directors, Royal Society of Medicine Foundation, Inc., 1971 to present (treasurer 1973 to present). Consultant and member, Coccal Expert Committee, World Health Organization, 1967 to present. Directors Council, New York Heart Association, 1973 to present. Chairman, Allergy and Immunology Study Section, National Institutes of Health, 1966–70. Commission on Streptococcal and Staphylococcal Diseases, U.S. Armed Forces Epidemiological Board (Deputy Director, 1968–72), 1963–72. Chairman, Research Study Committee and member, Executive Commission, Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association, 1963–66. Member, Policy Committee, American Heart Association, 1966–70. Board of Directors, New York Heart Association, 1967–73. Chairman, Advisory Council on Research, New York Heart Association, 1969–71. Research Committee, St. Louis Heart Association, 1963–66. Board of Directors, St. Louis Heart Association, 1962–66.

Editorships: Section editor, Journal of Immunology, 1974 to present. Editor, Journal of Experimental Medicine, 1973 to present. Editorial Board, Immunochemistry, 1973 to present. Editorial Board, Bacteriological Reviews, 1969–73. Editorial Board, Infection and Immunity, 1970 to present. Associate editor, Journal of Immunology, 1963–71. Editorial Board, Journal of the American Venereal Disease Association.

STATEMENT

Publications of more than 100 papers on research in infectious diseases and immunology.

Mr. Chairman and members of the committee, this is my first appearance before your committee as the new Director of the National Institute of Allergy and Infectious Diseases. I consider it a privilege to serve as spokesman for this fine Institute.

Before going into accomplishments and plans, I would like briefly to discuss two topics intinately tied to this Institute: first, the recent accumulation of knowledge defining "the immune system" and second, the Institute's primary role in unraveling the complexities of this system.

THE IMMUNE SYSTEM

Advances made over the past 6 or 8 years—largely with Institute leadership and financing—have led to one of the most significant developments in medicine: the recogntiion that several organs of the body function in concert as the immune system. I must digress for a moment to describe the immune system before discussing the diseases which occur when it does not function properly.

You are all famiilar with other organ systems, such as the cardiovascular system. Each is made up of several organs orchestrated to function together for a particular purpose. The recently defined immune system consists of the bone marrow, the thymus, the spleen, and the lymph nodes, as well as the white blood cells, as shown in the attached figure.

There is much yet to learn about the way the organs of the immune system work together in defense against disease. Much of our budget request is devoted to research toward this understanding. Because the organs are scattered throughout the body, they must have ways to communicate with each other. There is, indeed, a systematic traffic pattern of white blood cells moving from one organ to the other.

As shown in the attached figure, white cells originate in the bone marrow. Some migrate first to the thymus where they mature and acquire special characteristics. These are called T lymphocytes. Another type of cell, also originating in the

bone marrow, is known as the B lymphocyte. A third important white blood cell is the phagocyte, or "scavenger" cell. There is good evidence that all three cell types must interact for protection against disease.

When working properly, the immune system is the major defense against disease-causing microbes and other aliens, including malignant cells. It produces antibodies—protective blood proteins—to these aliens. Antibodies, plus phagocytes, lead to the destruction of agents causing disease. The immune system can be stimulated to do a better job. Vaccines are often used for this purpose. Other means of stimulation are being explored as in the immunotherapy of cancer.

Allergic and immunologic diseases occur when the immune system is deranged. There are many causes of this derangement. For example, an individual with a genetic defect may be unable to make antibodies. In other people, a very common derangement leads to allergies. Our Institute estimates that 1 out of every 6 Americans has a serious allergy. In these people, the immune system reacts abnormally to certain substances and produces an unusual kind of antibody. This antibody, termed IgE, triggers the release of harmful chemicals into the tissues of bloodstream. This series of events leads to asthma, hay fever, and other allergic conditions.

Disorders of the immune system are widespread and are responsible for various diseases, including kidney disease and arthritis. In ways not yet understood, there is reason to believe that these and other diseases are produced by certain persistent viral and bacterial infections.

Malfunction of the immune system is also frequently caused by potent drugs used to treat diseases such as rheumatoid arthritis and cancer. Patients given these drugs are very vulnerable to infections. Many cancer patients succumb not to cancer but to an overwhelming infection brought about by the drug-induced derangement of the immune system.

Related to this problem is our concern about hospital-associated infections. In a recent 4-year study, one-fourth of the patients dying at a large city hospital had an infection acquired in the hospital.

In discussing the immune system, I must comment upon the continuing relationship between it and the bacteria and viruses you and I encounter as we progress through life. The immune system is immature at birth and not primed to perform its protective role. Soon after birth, the nasal and upper respiratory passages and the intestinal tract becomes the home of millions of usually harmless microbes—bacteria and viruses—which stimulate the immune system to mature so it can protect us against the microbes which cause disease.

I mention this concept because it highlights the intimate relationship between microbes and the immune system. For this reason I believe that the National Institute of Allergy and Infectious Diseases is the logical home for the study of the immune system and how it functions. In my view, there must be primary responsibility in a single institute for this research. This is not to say that immunology is for one institute alone. Immunology is one of the basic disciplines, and the different institutes—such as Cancer and Arthritis—must draw upon these disciplines to solve their mission-oriented health problems.

CLINICAL IMMUNOLOGY

Recipients of kidney transplants have been "matched" to donors through the use of genetic markers. Methods to detect these markers have been developed largely through Institute-supported research. This Institute has also established the world's most complete serum bank for identification of these markers. This bank supplies reagents for tissue matching in more than 95 percent of the Nation's kidney transplants.

Further progress in transplantation is included in a special report. I should mention, however, work by Institute grantees at the University of Wisconsin and Wayne State University. These scientists have developed two new tests which will more accurately match a recipient and a cadaver donor kidney, thereby increasing the possibility of a successful transplant.

As the science of immunology has evolved, other extensive uses are being made of genetic markers. Materials provided by the serum bank are being requested for such purposes as blood platelet matching for cancer patients as well as for genetic studies of various diseases. The latter studies are among the most exciting in the field of immunology since it has been shown that individuals with certain markers have an increased susceptibility to various conditions, including multiple sclerosis and a form of arthritis affecting the spine. Both intramural and aca-

demic scientists are vigorously pursuing these new leads. We must increase our investment to develop and make available more typing sera if we are to meet the needs of these investigators.

ALLERGIC DISEASES

Asthma affects an estimated 9 million Americans. Research has indicated that asthma patients can be divided into several categories, each requiring its own particular form of treatment. One important advance this past year has been the use of inhaled atropine for one category of asthma patients. One of our asthma and allergic disease centers in Denver has proven the effectiveness of this new treatment in patients who no longer respond to steroids taken by mouth. The advantage is that the atropine acts directly on the bronchi to relieve the spasm of asthma. This is more effective than the older method of treatment and allows for smaller doses, thus minimizing undesired systemic effects.

More such studies are needed. Basic research has provided new information on the chemicals produced in the body which mediate the allergic response. Action of these chemicals might be blocked through use of properly designed drugs. We plan to pursue such leads with increased support.

There has been another achievement which takes us closer to understanding allergic reactions. Physicians for many years have given immunotherapy, or allergy "shots," to patients in an effort to desensitize those with serious asthma and hay fever. A team of grantees at Johns Hopkins University recently discovered that "shots" decrease the concentration of the special allergy antibody, IgE. At the same time, the symptoms of allergy are diminished or eliminated. This discovery should improve the success of "shot" treatment.

INFECTIOUS DISEASES

Influenza and other acute respiratory diseases.—The Institute has long recognized the need for better means of preventing and treating influenza and acute respiratory diseases. Influenza and pneumonia rank fourth as a cause of death and the acute respiratory diseases rank first in causing bed disability. A highly effective and widely used influenza vaccine could substantially reduce the 30,000 to 50,000 deaths which are associated with the major influenza epidemics. A better vaccine could also greatly reduce up to $700 million of direct costs for medical care during such epidemics. We plan to accelerate our efforts to develop live influenza vaccines and to improve present killed preparations.

Hepatitis.—An estimated 250,000 to 300,000 cases of viral hepatitis still occur annually. As many as half of these may be due to hepatitis B. Last year our Institute and the Heart Institute sponsored trials of a protective serum containing high levels of antibodies against hepatitis B. This serum promises to be useful in providing temporary protection for those at high risk.

A vaccine against hepatitis B would be more useful than the serum in high risk groups. We expect to complete safety and efficacy tests of a prototype vaccine in chimpanzees in the next 6 to 12 months and begin a cautious trial in a small number of volunteers soon thereafter.

Progress in hepatitis A is hindered by our inability to grow the virus in laboratory systems and our difficulty in obtaining specimens which contain the virus. Despite these obstacles, scientists have developed highly reliable blood tests for diagnosis of this form of hepatitis. These tests cannot be put to widepread use until we find new sources of the necessary reagents. We will expand our efforts next year to solve these problems.

Sexually transmitted diseases.—"Sexually transmitted diseases" is the newer, generally adopted, descriptive term for a group of diseases formerly referred to as venereal disease. These diseases are caused by a wide variety of infectious agents in addition to those causing syphilis and gonorrhea.

The Institute has steadily increased its research support of sexually transmitted diseases. In 1975, we established a third research center, located in Houston. We plan to increase our investment in this area of research and research training in 1977, including the establishment of still another center.

I would like to mention some of the recent work reported by our centers. Significant progress has been made on the problem of classifying strains of the gonococcus, the organism that causes gonorrhea—now the most common bacterial infection. One particular strain has been found to cause most cases of gonococcal arthritis. Efforts in the coming year will be directed toward providing a much

firmer serological classification system so we can develop a reliable blood test for gonorrhea and track its epidemic spread.

Nongonococcal urethritis appears to be twice as common as gonorrhea. As much as 50 percent of nongonococcal urethritis may be caused by unusual organisms, called chlamydiae. It is important to distinguish between gonococcal and chlamydial infections because each requires a different treatment. An expectant mother with chlamydial infection can transmit the organism to her child at birth, causing a serious eye disease.

Other organisms called mycoplasmas, are also possible causes of many nongonococcal urethritis cases, according to a recent report from the center at the University of Washington. In 1977, this search for the causes of nongonococcal urethritis and the development of suitable prevention or treatment will be one of our highest priority areas.

Bacterial meningitis.—An estimated 20,000 cases of bacterial meningitis occur in the United States each year—primarily in children under 5 years of age—and the number of cases seems to be increasing. Despite antibiotics a significant percentage of victims die. In newborns the death rate is nearly 50 percent. Among survivors there is an appreciable incidence of residual damage. Grantees at Vanderbilt University found that nearly 30 percent of children who survived meningitis had significant mental or neurological handicaps.

Our research is primarily directed at the prevention of meningitis. Meningococcus vaccines are now licensed but restricted to use in adults. We are working on similar vaccines for infants and children. A large field trial of meningococcus A vaccine is underway in children in Finland. We also are making plans with the Heart Institute to evaluate pneumococcal vaccines in children with sickle cell disease. These children are very susceptible to pneumococcal infections, including meningitis.

Viral diarrhea.—Several years ago a new virus associated with severe diarrhea in infants was identified by electron microscopy in the United States and other countries. Institute scientists who were among the discoverers of the new virus, have demonstrated conclusively that it causes diarrhea. Most important, they have succeeded in growing the virus in tissue culture—an advance that opens the way for the development of practical diagnostic tests and a vaccine.

GENETIC MANIPULATION

Recent news stories have recounted the efforts of scientists to transfer the genetic material, DNA, from one species to another. The compelling reason for continuation of this research is the intriguing and potentially useful new technology which may emerge—such as the capability to make pure insulin and other hormones cheaply in large-scale bacterial fermentation systems.

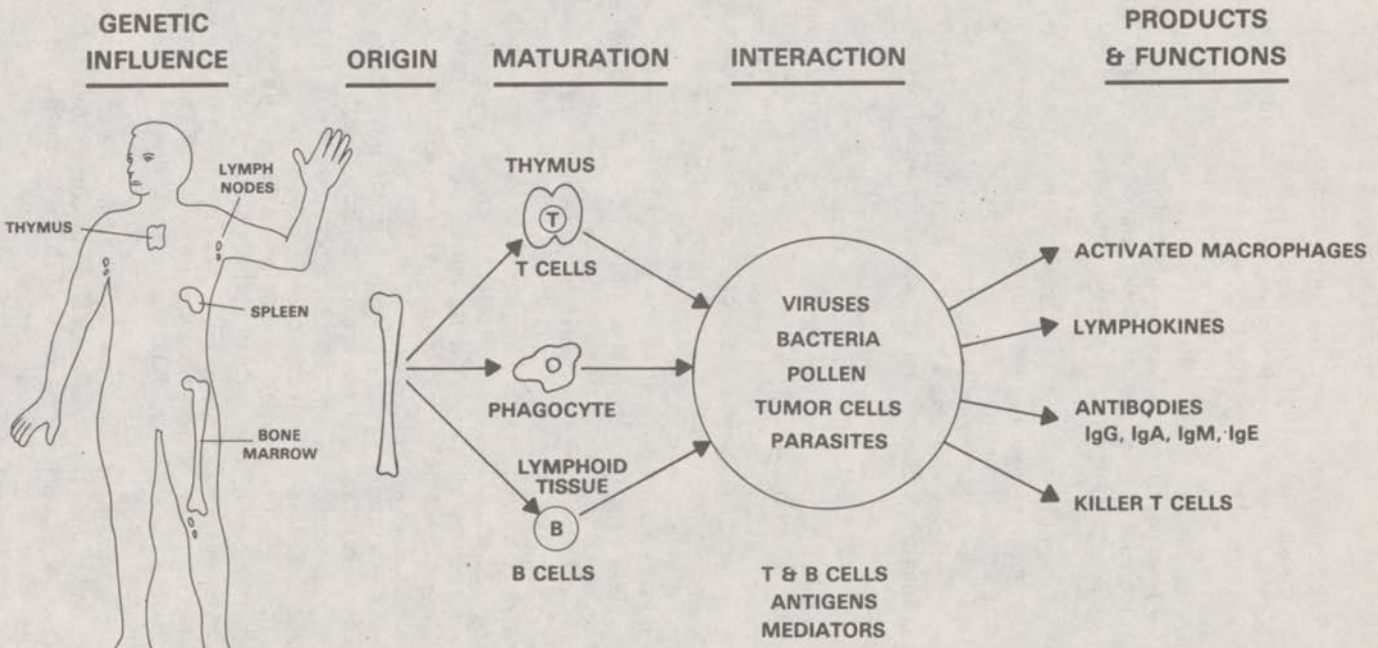
However, scientists are concerned about biohazards involved and have observed a voluntary moratorium on such work, pending agreement on safety standards. An NIH Advisory Committee has now proposed safety guidelines. The Institute will have a lead position in development of methods, materials, and rapid scientific communication which will enable this research to continue. We have requested funds to initiate this effort.

CONCLUSION

In closing, I wish to hark back to the immune system and its absolutely key role in the spectrum of infectious, allergic, and other immunologic illnesses. We are privileged to find ourselves at the very core of these exciting new developments that also hold so much promise to other areas of medicine. Our budget request for 1977 is $135,615,000.

Mr. Chairman, I have mentioned special reports. I would be glad to submit these for the record.

THE IMMUNE SYSTEM — A SIMPLIFIED VIEW



OPENING REMARKS

Mr. NATCHER. Would you like to point out anything in your statement before we start with the questions?

Dr. KRAUSE. There are a few things I think I might turn to briefly.

Mr. NATCHER. Doctor, go right ahead.

Dr. KRAUSE. First of all, this is my first appearance.

I am delighted to be the Director of this Institute. It is a fine Institute, and I am privileged to be its spokesman.

I think that I might just take several minutes, since I know you are running behind time, and I would emphasize two features of this statement.

First, I pointed out that this Institute is concerned with what we term "the immune system," and immunologic and allergic diseases that result when it malfunctions.

Second, we are concerned with recent progress in certain infectious diseases of special interest. These include influenza, hepatitis, the sexuality transmitted diseases, meningitis and others.

THE IMMUNE SYSTEM

Let me just take a moment or two to mention the immune system and what I mean by this.

You know of the other organ systems of the body, such as the cardiovascular system, the nervous system—which we have just heard about—and the endocrine system. Each of these is made up of several different organs orchestrated to function together.

We now know, as a result of the work of the last few years, of another system which we term the immune system. It is made up of the bone marrow, the thymus, the spleen, the lymph nodes, and the white blood cells. These work together in the defense against disease. Because they are scattered, the body has devised ways for these organs to communicate with each other. They communicate with each other by a traffic of cells streaming from one to the other.

When working properly, the immune system is our defense against disease caused not only by microbes, viruses, and bacteria, but also by other aliens, such as tumor cells.

When the immune system is deranged, we have disease such as allergic diseases; but there are others, including arthritis, diabetes, and chronic kidney disease, as well as the drop of the defense mechanism against other diseases such as cancer.

Let me make one brief comment about the immune system. It develops after birth, it is very immature at birth, but as a result of a constant exposure to the usually harmless bacteria that occupy our intestinal tract and our respiratory tract, the immune system is primed so it works much more effectively to mount the defense against diseases.

The relationship of bacteria and the human host has been a traditional concern of this Institute. The immune system is becoming recognized as an essential component of this relationship. Hence, I believe that the primary responsibility for study of the immune system should be with this Institute.

This is not to say others will not use immunology for the study of their special disease interests, but I do believe that there should be a special focus within the NIH for the study of the immune system.

INFLUENZA

Let me say that the statement does speak to several diseases, and I believe you have heard already about influenza.

I would say not only that we will do our best to improve the killed vaccine which is currently available, but we will also seek a better vaccine. We will push as far as we can on the research of the live influenza vaccine, which is similar to the Sabin polio vaccine.

We will watch the potential threat of swine influenza at Fort Dix by working closely with the Center for Disease Control, the Bureau of Biologics, and the Department of Defense on this potential threat. A special report has been prepared on respiratory disease.

HEPATITIS

We have research advances on both forms of hepatitis. These point the way to successful diagnostic tests for hepatitis A and the development of a hepatitis B vaccine.

SEXUALLY TRANSMITTED DISEASES

In sexually transmitted diseases, we have made I think important strides.

This is a new program only 4 or 5 years old, but much of the basic research is being done in order to bring this group of diseases under control.

GENETIC MANIPULATION

Finally, let me say that we are working on genetic manipulation. This is a new area in which the scientist envisions the possibility of taking the information that is needed for synthesis of insulin from the nucleus of a pancreas cell and then plugging it into the nucleus of a bacterium, so that bacterium in culture will be programed to produce insulin.

This is one of the examples that could come out of genetic engineering manipulation, but much needs to be done for safeguards against hazards. Our Institute will be working closely with the General Medical Sciences Institute on the developments of those procedures which will be needed for the implementation of this potent new development in biology.

There are the few opening remarks I would like to make. I believe you know our budget request, which is for $135,615,000.

PLAN FOR BUDGET INCREASE

Mr. NATCHER. Dr. Krause, you have made an excellent statement to the committee.

This 1977 budget for your Institute shows an increase, as you know, of $8,452,000 over the 1976 level. How do you plan to spend the increased funds?

Dr. KRAUSE. That is an important and good question, Mr. Chairman, and we are programing these in various areas.

First of all, as you might guess from my brief opening remarks, we have two aspects that we must be concerned with.

On the one hand, we must be concerned with the immune system and the diseases that result when it becomes deranged and on the other hand we must be concerned with the infectious diseases.

Let me remind you that the infectious diseases still rank fourth as the cause of death in the United States.

Therefore, it would be natural that we would direct attention to increased support for those diseases which are major causes of death or illness.

In the area of infectious diseases, we would increase our support for influenza research by nearly $1 million. We would be increasing our support for research on the sexually transmitted diseases. We know that, in addition to the two major ones of syphilis and gonorrhea, there are at least six or seven other major diseases transmitted in that way.

In addition, we would increase our activity in the study of the immune systems and its disorders by at least $2.4 million. This would include the work at the asthma and allergic disease centers. It would also include work on the basic and fundamental immunology needed to determine the way the immune system malfunctions in a variety of diseases, including kidney disease, arthritis, diabetes, and cystic fibrosis and cancer.

VENEREAL DISEASE RESEARCH CENTERS

Mr. NATCHER. Doctor, in the material that you submitted to the committee, you state that you are supporting three venereal disease research centers. What progress are these centers making in developing a simple and inexpensive screening test for gonorrhea?

Dr. KRAUSE. I might say I have some personal interest in that because I was at Rockefeller University before I came to Government and our laboratory there was involved in some of the initial work on the effort to develop a simple screening test.

Mr. NATCHER. Has one been developed, Doctor?

Dr. KRAUSE. We have a test, it is not yet a simple screening test which can be applied widely. I think, however, it is a first-phase test, which will lead us into the next phase of a test which would be much cheaper to use on a wide scale.

The test that we now have, which is an outgrowth of that development, as I said, at Rockefeller University, is now being tested in the field by the Center for Disease Control and we are encouraged by the results.

What we need now is the technology to reduce the cost.

VENEREAL DISEASE VACCINE

Mr. NATCHER. Do you believe that we will be able to develop a vaccine of this disease in the not too distant future?

Dr. KRAUSE. I think that we will need at least 1 or 2 more years of fundamental work on the organism, on the gonococcus itself, and on the way the immune system responds to infection before I can answer that question, in all honesty.

For example, we had the technological know-how to develop the meningitis vaccine about 6 or 7 years ago. We do not yet have the technical know-how we need for establishing and developing a gonococcal vaccine, but I am very hopeful that within a year or two we will have that scientific base. At that time we can then make the decision whether to move ahead with vaccine development.

DRUG INDUCED, IMMUNE FUNCTIONS

Mr. NATCHER. In your statement, doctor, you said that malfunction of the immune system is frequently caused by potent drugs used to treat diseases such as rheumatoid arthritis and cancer. Sounds like we have a "Catch 22" situation here. If we don't give the patient the drug they may die of cancer. However, if we do give them the drug they succumb to infection because of a drug-induced malfunction of the immune system. What about this problem, Doctor?

Dr. KRAUSE. Well, it is a problem and for those of us who have taken care of patients with arthritis, as I have done for 20 years before I came here, and other diseases of that sort, what you have to do is to steer a safe course as best you can. The drugs do lower the resistance against infection. Of this, there is no doubt.

At the same time, you are very careful in doing all you can to monitor the patient closely, make sure that all of the vaccines that you do have are given to prevent disease, to make sure that the patient is in close contact with you, so that if any hint of a problem develops you get at the problem early with an antibiotic treatment.

HOSPITAL-ASSOCIATED INFECTIONS

Mr. NATCHER. Doctor, also in your statement you said that one-fourth of the patients dying in a hospital during a given year had an infection of hospital origin, and that in 40 percent of these deaths this was the primary cause of death.

Dr. KRAUSE. Yes, sir.

Mr. NATCHER. This certainly does not speak very well for our hospitals. What kind of research do we plan to do in this area? Are you sure about your figures now, doctor, when you say 40 percent? Is that right?

Dr. KRAUSE. I think the statement was, in a recent 4-year study one-fourth of the patients dying at a large city hospital had an infection acquired in the hospital.

I think there are two factors that are involved in this. First, let me say it is an important question, and we should, indeed, come to grips with the issue of what we call the hospital-associated infection.

But, there are reasons for this figure being higher than it once was in the past, which is not all due to poor hygiene.

The two reasons are that we are doing many more invasive and surgical procedures on patients than were done in the past, such as intravenous feedings, in many instances for weeks, or intubation by feeding or other purposes. Many, many other things are done which provide a new portal of entry for infection into the body. In a sense, many of the things that we can do to combat different kinds of diseases

in a hospital, are things which make the patient susceptible to infection or to invasion.

The second thing is that the antibiotics which came upon us as the great miracle drugs 30 years ago have now turned out to be a two-edged sword. Whereas they are marvelously effective and they are, indeed, wonder drugs, the bacteria that cause disease have learned how to live around them. So many of the bacteria which are associated with hospital infections have developed resistance to penicillin and the other drugs.

Therefore, we do in fact have an extensive program to discover how the bacteria learn to become resistant to penicillin and our other drugs. I hope that as a result of our program we will be able to overcome their ability to become resistant to penicillin and other drugs.

NATIONAL NOSOCOMIAL INFECTION STUDY

Mr. NATCHER. Doctor, the Center for Disease Control conducts a continuous surveillance program called the National Nosocomial Infection Study. How do their efforts fit into what you are trying to do in regard to hospital infections?

Dr. KRAUSE. Well, I think that we rely very heavily on the Center for Disease Control for the kind of information that will tell us where the problems are, what kind of bacteria are the most common, the infection rate in patients that have had their prostates removed or have indwelling catheters. This is the kind of information that must be collected and is collected by the Center for Disease Control.

Once we have that information, we are then able to determine the science base that is needed for possible manipulation of the immune system to combat that infection or to do something about the acquired resistance to antibiotics that those organisms may exhibit.

We will indeed be working closely with the Center for Disease Control on this problem.

I have already had an official discussion with Dr. Sencer, who is the Director. And I have just, as you know, been at NIH for several months, but this is one of the areas on which we have touched base, and we will have another meeting on this in April.

TRANSPLANTATION

Mr. NATCHER. You made reference in your statement to matching of donors and recipients of kidney transplants through the use of genetic markers. Can you tell us a little more about this?

Dr. KRAUSE. Well, let's start with a simpler system, if we might for a moment. You all know that we each have a different blood type, there are four different blood types, and before you can have a blood transfusion you must be matched so that the person that gives you a pint of blood has the same blood type that you have.

What happens if you don't do that? If the blood given you is not the same type, your body's immune system recognizes it as a foreign substance, just as if it were a foreign bacteria or a cancer cell, and the body makes antibodies to those red blood cells that are transfused into you, and they are destroyed by those antibodies.

Now, if you type, so that you and your donor are matched and you receive the blood, it is accepted as your own, and circulates freely in the system.

Now, it was discovered, 10 to 15 years ago that not only blood cells, but also all of the other cells of our body, have signals on them which indicate that they belong to a certain type. In addition to just the several types of blood cells, we have at least 30 if not 50 different types to deal with when we deal with the tissues of our body, such as the kidney, the pancreas, or the bone marrow. So what we must do now is to make sure that the transplanted organ—whether kidney or bone marrow and whether cadaver or from a relative—is of the same type, just as the blood has the same type in a transfusion. When it does, the success of the transplant is much greater. The work that is going on now in the use of this typing system, and in which the Institute has taken a leadership role, clearly shows that with good matching the survivorship for the first 2 years goes up to something like 70 to 80 percent.

INFLUENZA VACCINES

Mr. NATCHER. Last year we talked with Dr. Davis about the need to develop influenza vaccines in order to be ready for the influenza epidemic of the late 1970's. Well, the problem seems to be right at our doorstep. What can you say to the committee about the development of a vaccine as far as influenza is concerned?

Dr. KRAUSE. First of all there are two aspects to the current flu problem. First there is a good deal of flu currently in the country now. This is all due to a variation of what we would call Hong Kong flu which first appeared in 1968. The current strain is what we called the Victoria strain.

The vaccine now being used will give some protection against this current epidemic flu strain. Because we know this current Victoria strain will still be around next year, causing influenza, it will undoubtedly get incorporated into the formulation of the killed vaccine for the coming season.

One of the problems will be to see to it that people take the vaccine. It has not been used as much as it should be. I think we are going to need to work with the Center for Disease Control, with professional societies, and with lay organizations to get acceptance of the flu vaccine.

I think it is a great credit to the Cystic Fibrosis Foundation, for example, that almost all children in this country have been vaccinated with flu vaccine, because that foundation has got behind the use of this vaccine. This is important because patients with cystic fibrosis are very prone to the development of pulmonary infections.

Such outreach mechanisms as that, I think, will need to be used to get the acceptance of the vaccine.

The second problem you referred to, I believe, Mr. Natcher, will be the possibility that there is a return of an influenza which might be similar to the 1918 influenza.

This has to do with several patients at Fort Dix who have been infected with a virus similar to what caused disease in 1918. We are

watching this very, very closely. Four agencies are involved in this, not only the NIAID but also the Center for Disease Control, the Bureau of Biologics and the Department of Defense.

We will monitor this week by week, and if it appears that this is something which will spread, rather than just subside as a minor incident, we will then need to make the decision to move into the vaccine preparation of this new virus.

One final comment. We are not content with the killed vaccine because we know it has limitations. For this reason we are striving hard out on the NIH campus as well as among our grantees to develop a live attenuated vaccine similar to the well-known and highly successful Sabin vaccine for the prevention of poliomyelitis.

ADDITIONAL FUNDS FOR INFLUENZA VACCINES

Mr. NATCHER. Doctor, I am going to ask you a question that you you might consider foolish but I am still going to ask you. If we were to give you additional funds for development of an influenza vaccine, would you be able to have such a vaccine ready by next year or do you just need time to evaluate what you presently know about the new strain of influenza virus?

Dr. KRAUSE. If you refer now to the strain at Fort Dix, at this juncture what we need is some time to find out whether this is a serious threat. If in the next few weeks we feel it is a possible potential threat, it would take additional funding, I am sure, in order to tool up so that sufficient vaccine incorporating the new strain could be produced for the population by next September or October.

Mr. NATCHER. Doctor, thank you.

VACCINE DEVELOPMENT

During the hearings last year, Dr. Davis told us that a pneumonia vaccine was in the final stages of evaluation. What is the status of that vaccine and when will it be widely available?

Dr. KRAUSE. The Kaiser Permanente Hospital in San Francisco under contract from the Institute is monitoring the occurrence of pneumonia in a large vaccinated population group. This is a controlled clinical trial. We expect sufficient data to be accumulated to enable definitive results to be published during calendar year 1977. These data together with data from trials in other countries should allow industry to obtain a license for pneumococcal vaccine within 2 years.

Mr. NATCHER. Doctor, in the material you submitted to the committee you indicated that a vaccine for hepatitis B is currently being tested on chimpanzees. When do you expect to initiate clinical trials for this vaccine?

Dr. KRAUSE. We expect to give the vaccine to about five or six persons beginning about a year from now. This will be a further test of safety before involving larger numbers of persons.

Mr. NATCHER. Another exciting vaccine that we talked about in the past is a meningitis vaccine. You mentioned that field trials are being conducted in Finland. What are the future prospects for this vaccine and when do you expect it to be available in this country?

Dr. KRAUSE. We expect the vaccine trials in Finland to be completed within another year. The meningococcal type A vaccine is currently a licensed product for use in adults in this country and as a result of the data from the Finland study, we would assume that the vaccine will be licensed by the FDA, for use in young children and infants, soon after completion of the trial.

RAGWEED ALLERGY

Mr. NATCHER. On Page 238 of your budget justification you say that an investigation of new drug application will be filed for the 3 purified antigens of ragweed. Can you give us a little more information about this and tell us what its implications are for the average person suffering from this type of allergy?

Dr. KRAUSE. These antigens at present are research tools to be used in exploring new diagnostic and therapeutic methods. Being purified, they elminate nonspecific results. If these prove to be advantageous, they should permit more exact determination concerning which pollens victims are senstive to and allow desensitization to these pollens.

Mr. NATCHER. When this drug becomes widely available—will it be expensive or will it be within the financial reach of the average person?

Dr. KRAUSE. If these purified pollen extracts become widely needed, industry should be able to produce them to replace the impure extracts now available without any material increase in costs.

TRANSFER OF GENETIC MATERIAL

Mr. NATCHER. Doctor, in your opening statement you make reference to research involving the transfer of genetic materials. Will you explain your Institute's role in this type of research?

Dr. KRAUSE. Mr. Natcher, I was referring to a new NIH program area which has the ultimate aim of determining the benefits which society might derive from the developing capability to transfer genes from one organism to another.

The NIAID role stems from the fact that it has supported a high percentage of the basic research which has opened up this new area. The size and diversity of our past interest is apparent when I tell you that in fiscal year 1975 we funded over $2.4 million in grants, contracts, fellowships, and intramural research. We have long been interested in what goes on inside bacteria and viruses and the genetic or inherited determination of such activities is a most exciting part of modern biology.

The most immediate problem in this area is that of safety and the NIH has assigned responsibility to the NIAID to insure that this work is able to proceed without undue hazard to the workers or the public. Our targeted contract program is intended to make research easier, quicker and safer. We are attempting to develop standard safer phages and plasmids that will provide the mechanism or vector for inserting nucleic acid into a standard and safer host—the bacterium E. coli. And we want to set up research and reference laboratories to test the range of genetic manipulations possible with new vectors and hosts

and also establish their safety by testing their ability, for example, ability to survive in nature if by chance they escaped from the confines of a laboratory.

Mr. NATCHER. I have consumed too much time.

I yield to you, Mr. Michel.

GORGAS MEMORIAL LABORATORY

Mr. MICHEL. Thank you, Mr. Chairman.

Doctor, in the past your Institute has instituted research at the Gorgas Memorial Laboratory. Does your request this year contain funds for continuation of this support?

Dr. KRAUSE. 1977 does not.

Mr. MICHEL. Why?

Dr. FREDRICKSON. Mr. Michel, I think maybe I can answer that. The Gorgas support, in the last several years, has come from the Fogarty International Center as well as from the Allergy Institute. This year you will note that the amount for Gorgas identifiable within the budget is $500,000, whereas actually the amount they will have received in this year is approximately $1,360,000.

We have discussed the Gorgas question, following the submission of the 1977 budget, with the Assistant Secretary for Health, and have examined carefully with the President of the Gorgas Institute their scientific potential and need for this year. We have requested some reprograming, without increasing the total of this budget. So that we can approximate the amount of support that Gorgas received in 1976. This will be approximately, depending on the figure, $1.4 million.

Mr. MICHEL. Is there any problem at all with the quality of the research conducted at the lab?

Dr. KRAUSE. I would like to just add to what has been said, and say that we know that one grant will be funded in the next fiscal year at Gorgas because one of the investigators, who is a qualified virologist, has a grant which has been approved at a level of about $150,000. We anticipate at least one other grant perhaps in the range of $70,000 will be funded. These are funds in addition to those that Dr. Frederickson has talked about.

Mr. MICHEL. Would you address yourself more specifically to that last question, and that is, is there any problem with the quality of the research at that lab?

Dr. FREDRICKSON. There is no question that Gorgas has a distinguished history of research in tropical diseases. It is an important facility; it is working on problems like malaria that are very important in that area. We have available to us certain reports of the advisory committees that Gorgas itself has put together. They include certain members of our staff. I think that they are doing a good job maintaining a staff there in the face of increased costs. It has been a difficult job for Gorgas.

We are interested in continuing to examine carefully and regularly, their scientific activities and their potential, so that we can feel that we have the best possible base for support for them which, under the current arrangement, is primarily through the Fogarty International Center.

Any additional contract research support which they might get through the Allergy Institute would, of course be subject to the standard review mechanisms.

UNITED STATES-JAPAN PROGRAM

Mr. MICHEL. NIH supports a number of international programs, and one is that United States-Japan program focusing on selected diseases of major health importance to Asia. How much is spent for this program by the United States and by Japan?

Dr. KRAUSE. In 1976 we will be spending $5,276,000.

Mr. MICHEL. Up or down from 1975.

Dr. KRAUSE. That is down by $1.2 million.

It should be made clear how the program works. A small portion of that money is spent abroad but not to fund Japanese investigators and only a few third country investigators. The bulk of that money is spent within the United States and is given to investigators who have submitted grants working in the areas of emphasis. Those grants are handled in the same way as regular grant applications. They are evaluated on the basis of quality and merit.

If they are in the fundable category because of a sufficiently high priority score, they then get funded for certain diseases. An example is the viral disease dengue, which is a major problem in Asia but also one which is again becoming a problem in the Western Hemisphere. Particularly there have been some recent outbreaks in Puerto Rico.

In addition, tuberculosis is one of the areas on which they concentrate, and I should say we had about 3,500 deaths due to tuberculosis in the United States last year. Out of this program have come some other things, for example a possible new approach to the treatment of cancer by giving to patients the tuberculosis vaccine BCG. This is an extensive program in which we participate with the Cancer Institute in fractionating the tuberculosis organism to try to determine which component has the antitumor quality. We are, of course, working on some of those diseases that are specific problems for the developing countries, as indeed we should, and these include schistosomiasis and the other parasitic diseases as well as the bacterial disease, cholera.

FUNDING OF UNITED STATES-JAPAN PROGRAM

Mr. MICHEL. Since I asked you what our contribution was this year compared to last, I think we ought to have the last several years of that Japanese contribution too, year for year.

Dr. KRAUSE. We will certainly provide it, sir.

[The information follows:]

UNITED STATES-JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM DIRECT RESEARCH FUNDING

United States:	
Fiscal year:	
1974	$7,150,126
1975	6,610,283
1976 (estimated)	5,276,000

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No official estimates are available from the Japanese Government and in any case it is difficult to make estimates comparable to the U.S. expenditures because of fundamental differences in the patterns of support by the respective countries. For example, direct grants in Japan generally come from both the Ministry of Education and the Ministry of Health and Welfare but do not include personnel costs—which are 50 percent to 80 percent of a U.S. grant budget. Nor do the Japanese grants provide for total costs—analogous to U.S. indirect costs; these are allowed for through institutional budgets.

We estimate the direct grant support by the Japanese to be about $500,000 in calendar year 1976. Although this appears substantially less than that of the United States it is comparable based on such considerations as gross national product, population and percent of the national budget devoted to support of science and technology. More importantly, the scientific contributions of the Japanese at the various joint meetings and conferences have been of a volume and quality that insures the viability of the agreement and the continuing enthusiastic cooperation of U.S. scientists.

Mr. MICHEL. So you would say we do have some direct benefits to the American people as a result of this research even though it is a pooling of Japan and the United States supposedly to delve into some of these particular diseases of Asia?

Dr. KRAUSE. Yes, sir.

Mr. MICHEL. Is it confined to that?

Dr. KRAUSE. The diseases are those which have an interest in Asia but as I said they also are problems here. We have the problem of tuberculosis in this country. We have the problem of some of the vital diseases as they are concerned with, including dengue, which is now right at our doorstep. It is true some of these diseases are primarily in other areas of the world. On the other hand, the United States, as you know, has responsibilities elsewhere, and we have a considerable percentage of our people as well as our military stationed in areas of the world where these diseases are a problem.

INTERNATIONAL PROGRAMS

Mr. MICHEL. Are there any other international programs to which your Institute lends support to combat problems of this country or diseases of the country?

Dr. KRAUSE. We have, I would say, just a loose liaison with the Soviet Union, particularly in terms of the monitoring of the spread of flu and the development of flu strains.

Mr. MICHEL. When you say loose, you mean there is no mixing of funds; they go their way and we go ours?

Dr. FREDRICKSON. Yes, but it is an organized relationship through the U.S.-U.S.S.R. medical research program.

Dr. SEAL. They have meetings between U.S. scientists and Soviet scientists.

Mr. MICHEL. I won't take any more of your time.

Dr. KRAUSE. I should mention the cholera research laboratory in Dacca, Bangladesh, to which we have a managerial input.

Mr. MICHEL. You might expand on the record.

[The information follows:]

INTERNATIONAL RESEARCH PROGRAMS

Research supported or conducted by the National Institute of Allergy and Infectious Diseases includes many diseases which constitute minor health problems in the United States but have a large socioeconomic, health status, and political

impact on other countries. Because of the universality of biomedical processes these diseases provide unique scientific opportunities to gain information and insight on diseases of prime importance to the United States. These research activities, plus support of U.S. scientists in fellowships abroad, also provide unusual and unique opportunities for training of U.S. scientists.

The Institute has no bilateral agreements with any foreign nation nor does it have a lead agency designation in any agreement. It does, however, channel funds, consultative advice, and exchange of personnel by means of a variety of existing agreements between the State Department or other Federal agencies and a counterpart level in a number of foreign countries. Agreements may be broad, such as U.S.-U.S.S.R. Cooperative Health Agreement which includes a facet of biomedical research—such as influenza with the Center for Disease Control as lead agency—or relatively formal and focused on specific areas of biomedical research—such as the U.S.-Japan Cooperative Medical Science Agreement. In addition, there are broad country-to-country cultural exchange agreements which permit the use of Public Law-480 funds—so-called blocked funds. Cultural exchange agreements exist with India, Egypt, Poland, and Yugoslavia. The Public Law-480 funds can be used to support biomedical research projects performed by individual foreign researchers in collaboration with an NIH or U.S. academic scientist. These studies often have direct application to U.S. disease problems. For example, in Egypt there are excellent studies on streptococcal and meningococcal infections—both major problems of infectious disease in the United States. In India and Poland there have been studies on the organisms causing tuberculosis and gastroenteritis, the latter disease an important cause of disability and death in children.

Under Public Law 86-610 a program of international centers for medical research was established by the NIH "to advance the status of the health sciences in the United States and thereby the health of American people" by expanding collaborative research between U.S. universities and selected foreign institutions. Since 1968, this program has been administered by the NIAID and currently comprises awards to four U.S. institutions, who in turn, have established overseas bases with collaborating foreign institutions. These are: Johns Hopkins University and Cholera Research Laboratory, Dacca, Bangladesh; University of Maryland and the Institute of Hygiene, Lahore, West Pakistan; University of California and the Institute for Medical Research, Kuala Lumpur, Malaysia; Tulane University and Universidad del Valle, Cali, Colombia.

In addition to the programs of research supported under some form of international agreement, as mentioned above, a limited number of foreign grantees directly receive regular research grant awards for support of projects with exceptional merit.

Much more detail on international research and training will be found in the NIH Annual Report of International Activities to be published by the Fogarty International Center in the early summer of 1976.

HOSPITAL-ASSOCIATED INFECTIONS

Mr. MICHEL. You touched on that question of the one bad hospital where the chairman detected those hospital infections but in closer reading of your testimony I see it was just one hospital where this was 25 percent. While that might be a very extreme one and deserving of mention, is it all that bad?

Dr. KRAUSE. I think it would vary greatly, sir, depending upon the specialization of the hospital. Certainly a cancer hospital would be undoubtedly worse because they are using so many of these drugs. Also within a large hospital it would vary from one section to another. In abdominal surgery—because you do get into the bowel—you have a high rate of infection. Surgery of the urinary tract has a high rate. On the other hand, there are many other areas in the hospital in which it is low. So the figure is put for emphasis and not as an overall reflection of the problem.

SERUM FOR HEPATITIS

Mr. MICHEL. You make reference in your statement to a serum designed to protect against hepatitis. Where are we with regard to that serum, and how long might it take before we might expect widespread usage of that?

Dr. KRAUSE. That serum is now being tested for its efficacy, and we have done cooperative trials with the Heart and Lung Institute. I think it is promising. It will be one which is used only on a limited scale. It would be useful for the staff of dialysis units and useful for those who have been exposed or otherwise at high risk, those who are working in institutions such as those for the mentally retarded.

That antiserum will be of use, but of course the next important step is the development of a vaccine.

COST OF VENEREAL DISEASE RESEARCH

Mr. MICHEL. If I might move on then to the area of venereal disease that the chairman had a series of questions on. Do we have the exact total dollar amount in the venereal disease research effort in the record here?

Dr. KRAUSE. I think you have, sir. The Center for Disease Control has submitted a special report, prepared jointly with our Institute. It indicates that for 1977 the CDC funding will be in the neighborhood of $28 million, and the National Institute of Allergy and Infectious diseases funding would be about $6,134,000.

Mr. MICHEL. Correct me if I am wrong. Are we doing more in research than actual delivery?

Dr. KRAUSE. No; obviously a great deal of what the Center for Disease Control does is in delivery and control. I should not have spoken to their testimony.

Mr. MICHEL. Right.

Dr. KRAUSE. Just our own is a little over $6 million. Last year—fiscal year 1976—it was estimated at about $4 million.

MATURITY OF IMMUNE SYSTEM

Mr. MICHEL. You indicated the immune system is immature at birth. When does it achieve full maturity?

Dr. KRAUSE. It achieves full maturity I would say—we don't have enough information, but let's say 12 to 14 years of age.

For example, you all are familiar with streptococcal infections or strep sore throat. These are infections which start at about the fifth year of age, and we have them quite frequently until we are 12 or 13 years old, and then the rate drops. One of the reasons is that the immune system has matured by that time, so it can counter those infections and from then on they are much less common.

Mr. MICHEL. Are any other institutes studying this immune system? Is it a tug of war?

Dr. KRAUSE. It is not so much a tug of war as an exciting rugby game, and there are other institutes, of course, concerned with this. As I mentioned, the immune system is a system which, when it is deranged, can result in kidney diseases, nephritis, and rheumatoid arthritis. When it is not functioning properly, it is a leading factor in the

occurrence of cancer. So there is research going on in the Cancer Institute, in the Arthritis Institute. I don't have the figures in front of me, but I do believe at this juncture, at least in grants, we are currently funding about, I would say, three-sevenths of the grant research in the immune system.

Mr. MICHEL. I ask that because you appear to be a little bit defensive in your statement on that, but I think you have pretty well clarified. That is probably as good a place to lead into that series of questions I have asked the directors of all the other institutes, Doctor, if you will be good enough when they are inserted in the record to respond.

[These materials on peer review appear in the testimony of the NIH Director.]

Mr. MICHEL. Thank you, Mr. Chairman.

VACCINE TRIALS ON HUMAN VOLUNTEERS

Mr. ROYBAL. Mr. Chairman, I only have two questions, and due to the lateness of the hour I will not extend it beyond that. I am interested in knowing something about your new vaccine you are trying on a few volunteers. Are they in fact volunteers or did someone volunteer them?

Dr. SEAL. These are truly volunteers.

Mr. ROYBAL. Not like they used to do in the Army?

Dr. SEAL. No, sir. These are mostly at the University of Maryland Hospital in Baltimore. They are mostly college students, although some are people who for other reasons are willing to spend 1 week or 2 weeks or 3 weeks in isolation after their challenge with the flu virus. They come as a result of rather wide publicity. They seek out the hospital or the investigative group and say, "We would like to volunteer." They are then screened. The screening includes an interview by a psychologist and others before the doctor ever sees them, in terms of their motivation to be a volunteer.

They are basically free-living people that come and say, "We would like to do this," after they hear about it.

Mr. ROYBAL. Will we ever know who these volunteers are after the vaccine is developed, and we are grateful for the fact that it has been? Because I am sure science has used volunteers in the past, and I don't remember learning the names of volunteers or the progress that has been made.

Dr. SEAL. Most often they are quite anonymous. There are a few that have been famous in Walter Reed's yellow fever experiments. By and large, most of them have been anonymous, and I think in this case, where you deal with large numbers over a period of time, they will probably come out to be anonymous unless something unique happens.

Mr. ROYBAL. I would like to know how many men there are, how many women, and even try to find out their background.

Dr. SEAL. We can provide this for the record.

Mr. ROYBAL. I would also try to get the results of the test. For instance, was a person from a particular background more immune than someone from another background? I think that would be interesting information.

Dr. SEAL. Yes, sir.

[The information follows:]

The major facility used for volunteer studies with influenza vaccines is at the University of Maryland Hospital in Baltimore. This is operated by contract with the department of medicine of the medicaid school. Volunteers are recruited mostly through the schools in the Baltimore area. With the concurrence of school authorities, recruiters have been abled to publicize the volunteer facility, the work done, and the need for volunteers by placing ads in school papers, posters on bulletin boards, meetings with student government leaders and lectures. Advertisements are also placed in the Sunday newspapers. Meetings are arranged with groups of individuals who make inquiry. After further explanation of the program and of what a volunteer may be asked to do, names are taken of those still wishing to be considered. Further screening is carried out to determine suitability and if the volunteer passes this screening they are entered into a pool of names from which volunteers are obtained for the individual experiments.

In the year ending June 1975 a total of 547 volunteers entered into the volunteer pool. Of these 311 were male and 236 were women. Of these 70 actually participated in studies. These 70 were drawn from the University of Maryland, University of Baltimore, Johns Hopkins University, Towson State College, Howard County Community College, Catonsville Community College, Loyola College, and Charles County Community College. Four volunteers had not completed high school, 30 were high school graduates, 19 college undergraduates, 12 college graduates, 4 had master's degrees and 1 a Ph. D. Fifty-nine were white, nine black, one Indian, and one Chinese American.

Data are not available on socioeconomic level of the family but most would be middle to upper class since these are mostly college students or headed for a college education.

There is no suggestion that there are differences of immunity within the relatively narrow age and socioeconomic background represented.

GUIDELINES ON GENETIC MANIPULATION

Mr. ROYBAL. Second, with regard to the genetic manipulation, you have indicated there is a moratorium pending issuance of some new guidelines. Will you provide for the record what those guidelines are?

Dr. KRAUSE. Yes. I think Dr. Frederickson should answer that question because they are NIH guidelines.

Dr. FREDRICKSON. Just very briefly, the moratorium, which is voluntarily engaged in by American scientists and others around the world, is still in effect. The data which NIH put together about a year ago to develop guidelines for this exciting and important research have been submitted to me as the Director of the National Institutes of Health. We have had a public hearing with regard to those guidelines and the final guidelines, and my comments upon them, will be developed as soon as it is possible to do justice to the public record and all the considerations.

I would hope that we can present the final guidelines—at least as final as they will be for now because this is a changing field—about April 1.

Mr. ROYBAL. But these guidelines are being developed not by one person but by a group of people.

Dr. FREDRICKSON. Yes, sir. We can submit to you the present guidelines but they are not yet approved.

Mr. ROYBAL. Once they are all approved I think the committee would like to have those.

Dr. FREDRICKSON. We will see that the committee has a full record.

Mr. ROYBAL. The main point is that they are being developed by a committee of experts, not just one individual.

Dr. FREDRICKSON. That is correct, and now by a committee of non-experts including the Director of NIH.

Mr. ROYBAL. Thank you very much, Doctor.

When one says he is not an expert, that means you are really.

I thank you for your testimony. It has been most enlightening.

Mr. NATCHER. Mr. Conte.

CONTRACT VERSUS GRANT DOLLARS

Mr. CONTE. What portion of your research is done on a contractual basis, what portion by grant, and how does this compare with last year?

Dr. KRAUSE. In fiscal year 1976 we estimate that 10 percent of the research supported by the Institute will be done by contracts and 59 percent by research grants. The comparable figures for fiscal year 1975 would be 11 percent by contract and 58 percent by research grants.

OVERLAP OF EFFORT

Mr. CONTE. To what extent does the work done at NIAID overlap other Institutes and groups such as Center for Disease Control?

Dr. KRAUSE. We do not, of course, duplicate the work of other Institutes. In some areas we actively collaborate as in some aspects of research on viral heptatis with the National Heart and Lung Institute and the Bureau of Biologics/Food and Drug Administration. In other areas we work on different mission related aspects of the same broad problem, for example, slow virus infections, an interest also of the National Institute of Neurological and Communicative Disorders and Stroke. We continue to work closely with the Center for Disease Control in specific areas such as hepatitis and influenza. Their scientists are in touch with ours through workshops, planning groups, and collaborative or contract projects of mutual interest. We also depend on CDC for up-to-the-minute information on the epidemiology of selective diseases across the Nation and for alerts to potentially dangerous changes in disease patterns.

LINK BETWEEN NERVOUS SYSTEM AND IMMUNE SYSTEM

Mr. CONTE. Is research being undertaken to explore the possible links between the nervous system and the immune system?

Dr. KRAUSE. There are at least three lines of investigation. One has to do with the infections of the central nervous system by bacteria such as the meningococcus or viruses such as St. Louis encephalitis. Another pursues the more complicated interaction between a bacterium such as leprosy which infects the peripheral nerves and through an immunologic reaction, probably a hypersensitivity reaction, causes damage to the nerve. Similarly, the so-called autoimmune reactions that cause allergic encephalomyelitis result from direct harmful interaction of the immune system with central nervous system tissue.

IMMUNOTHERAPY IN CANCER PATIENTS

Mr. CONTE. How closely is NIAID working with the Cancer Institute to eliminate negative reactions to immunotherapy in cancer patients?

Dr. KRAUSE. A major problem with cancer patients under intensive treatment is their susceptibility to infection, often with organisms that have little pathogenicity for the rest of us. Perhaps 25 percent of the patients who die of cancer have a serious infection at the time of death. This unusual susceptibility seems to be directly related to the depression of the immune system response. NIAID has two broad interests—one has to do with research on better methods for prevention and treatment of infections with vaccines or antibiotics. The other has to do with selective augmentation or manipulation of the immune system. There has been a close collaborative effort between intramural scientists of both Institutes. The thrust of this effort is to find ways of stimulating the immune system to recognize and destroy the alien tumor cells. There is also extensive collaboration in virologic research especially in relation to leukemia.

ALLERGY ANTIBODY I_gE

Mr. CONTE. Can you explain for us the benefit of the recent advance dealing with the allergy antibody I_gE?

Dr. KRAUSE. The discoveries regarding I_gE have at least two immediate benefits to the patient. The level of I_gE can be measured and used to follow the effectiveness of desensitization "shots" for treatment of allergies. And the reaction of I_gE with a specific antigen can be used in an immunological test called the RAST test to determine precisely which of several antigens may be the true allergic offender.

INFLUENZA VACCINE

Mr. CONTE. In the opening statement, Dr. Krause, you stated that "A highly effective and widely used influenza vaccine could reduce the 30,000 to 50,000 deaths which are associated with flu epidemics." Is there such a vaccine?

Dr. KRAUSE. I want to give a helpful, positive answer but I also want to avoid overpromise in a complicated situation that despite much study still has serious constraints and significant unknowns. We know how to produce commercially an effective influenza vaccine. But to a considerable extent we are at the mercy of chickens and their spring egg-laying patterns and, of course, constrained by the time required for production of 50 to 100 million doses of vaccine from those eggs and its acceptance by the public and its administration by physicians in a short time frame, roughly September, October, November.

These production and delivery problems are really beyond the ken of this Institute. We have our own research problems with the virus. We are always playing a game of catchup with the influenza virus which changes or drifts in its antigenic composition somewhat from season to season. The decision on what virus strain to put into the vaccine to be used next fall is normally made in December or January.

Right now, the virus responsible for most influenza in the United States is closely related to the A/Victoria strain. This strain is not in the vaccine currently available. A/Victoria would have been a hands-down choice for the coming vaccine production season and for use next fall except for the fact that swine influenza strains have just been rec-

ognized as the cause of human infection at Fort Dix, N.J. This is a radically different type A influenza virus. Right now, there is no concensus as to what strain should be used in the new vaccine—A/Victoria or A/swine or both. Investigations both epidemiological and laboratory, now in progress, should provide the data necessary for decision within a few weeks.

But there is another problem to giving a simple, forthright answer to your question. Many of these deaths fall into the category of excess mortality deaths especially in the older segment of our population. Put simply, this means that the victims are not reported as dying of acute influenza but of cardiovascular, renal, or other respiratory disease. But excess mortality is not a vague concept that we can ignore. It is a very real thing proven by years of epidemiologic research and made manifest only in retrospect when we look back over the pattern of deaths during the year. We know that vaccination can prevent most clinical cases of acute influenza and hence reduce markedly the socio-economic impact of simply being sick. We think that vaccination will prevent the damage by the acute influenza virus infection that subsequently leads to excess mortality. But we haven't been able to prove that scientifically. In addition to the beneficial effect vaccination has for the individual, it certainly will reduce the total number of influenza cases and hence the risk of transmission from human to human and probably therefore the amount of excess mortality. This is the concept of herd immunity and obviously depends upon how widely the vaccine is used in the herd. I hope the population of the United States does not take offense to this term.

Mr. CONTE. How significantly could such a vaccine reduce these deaths?

Dr. KRAUSE. A vaccine produced by modern technology, well matched antigenically to the virus circulating among the population, and administered widely and in a timely fashion should have an efficacy of 70 percent or better.

SERUM FOR HEPATITIS B

Mr. CONTE. How long do you expect it to take before there are definitive results on humans of the protective serum for hepatitis B?

Dr. KRAUSE. The data from several comprehensive trials in which we, National Heart and Lung Institute, Bureau of Biologics and the Veterans' Administration all played a role are now in hand. Statistical evaluation of this data should be complete in another 6 months or so.

NONGONOCOCCAL URETHRITIS

Mr. CONTE. Exactly how widespread is nongonococcal urethritis?

Dr. KRAUSE. Nongonococcal urethritis is reported from every part of the United States. Its incidence is believed to be at least twice that of gonorrhea, but this is based on various sampling procedures since the reporting of this disease by private physicians is not very reliable.

BACTERIAL MENINGITIS

Mr. CONTE. Do you forsee any relief in sight for the 50 percent death rate among infants with bacterial meningitis?

Dr. KRAUSE. We are optimistic about several research and development approaches to this complicated problem. Most bacterial meningitis is caused by one of five organisms. In neonates, that is infants up to 1 month of age, group B streptococci and E, coli cause the great majority of disease. We cannot hope to immunize effectively infants this young. Their immune systems are two immature to respond well and we haven't the timespan available to vaccinate and protect. But we do have some evidence that if the mothers have antibody the offspring don't get meningitis of this type. It is conceivable that mothers-to-be could be vaccinated; but this is all very much in the research phase. Children in the age range of 1 to 12 months are also difficult to immunize at least with current H. influenzae or pneumococcal vaccines; although meningococcal type A vaccine appears to be immunogenic even down to 3 months of age. Older children from 18 months to 6 years would seem to be the prime target for vaccination with current meningococcal type C, H. influenzae, and pneumococcal vaccines. These three vaccines are in an advanced development and evaluation stage. There is already some possibility of more immunogenic vaccines, including meningococcal type B vaccine, but these are in the research phase of study.

NIAID STAFFING

Mr. CONTE. I have become very concerned about the number of positions at NIAID. My figures show that since 1967 the permanent full-time budgeted positions has declined from 751 to 587. Why has there been such a drop?

Dr. KRAUSE. The position cut was imposed on the Institute from above, so I can only guess as to the reasons. I think the drop may reflect the impression that infectious diseases are no longer a major health problem in the United States because smallpox, measles, polio, and other similar diseases are under control. Although hepatitis, influenza, pneumonia, meningitis, and venereal diseases still remain extremely serious problems, priorities must be established within the personnel resources available to the National Institutes of Health. These priorities are in the catastrophic disease areas such as cancer, stroke, and heart disease which are currently the center of public interest.

Mr. CONTE. Where have you cut back to arrive at this number of positions?

Dr. KRAUSE. We have had to eliminate field stations in Atlanta, Ga., and the Panama Canal Zone and seriously reduce the number of positions at Rocky Mountain Laboratories as well as our laboratories in Bethesda. Research on encephalitis, rabies, and tropical and insect borne diseases in general have been reduced or eliminated. New activities in hospital-acquired infections and sexually transmitted diseases have been delayed and most importantly we have been unable to satisfactorily pursue research on the immune system.

IMMUNE SYSTEM BUDGET

Mr. CONTE. What is your professional judgment budget for the immune system category?

Dr. KRAUSE. We feel there is a need for $58,250,000 to fund the most important leads in this area. However, I recognize that there are competing national priorities for scarce resources which must be considered by the administration and Congress.

Mr. NATCHER. Thank you gentlemen, that is all.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation[1/]

	1976	1977
Appropriation	$118,918,000	$135,615,000
Request pending	7,934,000	---
Subtotal, adjusted appropriation	126,852,000	135,615,000
Comparative transfer from:		
"Office of the Director, NIH" for Standard Level User Charges	311,000	---
Total, obligations	127,163,000	135,615,000

1/ Excludes the following amounts for reimburseable activities carried out by this account: 1976 - $550,000; 1977 - $550,000.

National Institute of Allergy and Infectious Diseases

Budget Mechanism

	1976			1977		
	No.	FTE	Amount	No.	FTE	Amount
Grants						
Regular						
Noncompeting	959	---	$57,417,000	728	---	$52,987,000
Competing	100	---	9,313,000	222	---	13,293,000
New	41	---	2,726,000	161	---	8,862,000
Supplemental	(8)	---	100,000	(8)	---	100,000
Subtotal	1,100	---	69,556,000	1,111	---	75,242,000
Special						
Scientific evaluation	5	---	235,000	5	---	284,000
International centers for medical research	4	---	2,400,000	4	---	2,400,000
Research career program	87	87	2,265,000	95	95	2,624,000
Subtotal	96	87	4,900,000	104	95	5,308,000
Total grants	1,196	87	74,456,000	1,215	95	80,550,000
Fellowships						
Noncompeting	116	164	2,593,000	208	232	3,061,000
New	145	145	1,818,000	152	152	1,900,000
Subtotal	261	309	4,411,000	360	384	4,961,000
Training grants-						
Noncompeting	50	225	3,523,000	22	88	2,000,000
Research and development contracts	132	---	12,341,000	145	---	13,961,000
Intramural laboratory & clinical research	---	---	25,069,000	---	---	26,598,000
Program management	---	---	249,000	---	---	271,000
Other direct operations	---	---	6,803,000	---	---	6,872,000
Standard level user charges	---	---	311,000	---	---	402,000
Total			127,163,000			135,615,000

DHEW - National Institutes of Health

CROSSWALK - 1976 Column of 1977 Justification

INSTITUTE: National Institute of Allergy and Infectious Diseases
(Dollars in thousands)

Program \ Mechanism	Research Grants			Training Programs		R&D	Lab & Clin	Other Direct	Program	
	Regular Programs									
	Noncompeting	Competing	Specials	Fellowships	Trg. Grants	Contracts	Research	Operations	Management	Total
Allergic & Immunologic Diseases.	$22,051	$4,273	$1,594	$1,764	$1,163	$2,500	---	---	---	$33,345
Infectious Diseases.	35,366	7,866	3,306	2,647	2,360	9,841	---	---	---	61,386
Intramural Research and Direct Operations	---	---	---	---	---	---	$25,320	$6,863	---	32,183
Program Management	---	---	---	---	---	---	---	---	$249	249
Total obligations	57,417	12,139	4,900	4,411	3,523	12,341	25,320	6,863	249	127,163

DHEW - National Institutes of Health

CROSSWALK - 1977 Column of 1977 Justification

INSTITUTE: National Institute of Allergy and Infectious Diseases
(Dollars in thousands)

Program \ Mechanism	Research Grants			Training Programs		R&D	Lab & Clin	Other Direct	Program	
	Regular Programs									
	Noncompeting	Competing	Specials	Fellowships	Trg. Grants	Contracts	Research	Operations	Management	Total
Allergic & Immunologic Diseases.	$20,376	$8,409	$1,777	$2,049	$550	$2,900	---	---	---	$36,061
Infectious Diseases.	32,611	13,846	3,531	2,912	1,450	11,061	---	---	---	65,411
Intramural Research and Direct Operations	---	---	---	---	---	---	$26,923	$6,949	---	33,872
Program Management	---	---	---	---	---	---	---	---	$271	271
Total obligations	52,987	22,255	5,308	4,961	2,000	13,961	26,923	6,949	271	135,615

Summary of Changes

1976 Estimated obligations	$127,163,000
1977 Estimated obligations	135,615,000
Net change	+8,452,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of pay raise	---	$365,000	---	$+137,000
2. Within grade increases	---	198,000	---	+109,000
3. Wageboard pay increase	---	561,000	---	+80,000
4. Variable incentive pay	---	517,000	---	+59,000
5. Postage rate increase	---	138,000	---	+20,000
6. FTS rate increase	---	108,000	---	+25,000
7. Travel rate increase	---	420,000	---	+60,000
8. Increased cost of employees compensation fund	---	25,000	---	+5,000
9. Increased cost of service and supply	---	2,700,000	---	+88,000
10. Payment to NIH Management Fund	---	9,565,000	---	+1,000
11. Standard Level User Charges	---	311,000	---	+91,000
Subtotal				+675,000
B. Program:				
1. Research Grants				
a. 41 new and 177 competing renewal awards in 1976 and transition quarter converted to noncompeting in 1977 - regular program.	---	57,417,000	---	+17,841,000
b. 161 new and 222 competing renewal awards in 1977	---	12,139,000	---	+22,255,000
c. Continuation cost of special program - scientific evaluation	---	235,000	---	+49,000
d. 10 new special program - research career program.	---	---	---	+400,000
2. Training Programs				
a. 145 fellowship awards in 1976 converted to noncompeting in 1977.	---	2,593,000	---	+1,891,000
b. 152 new fellowship awards in 1977.	---	1,818,000	---	+1,900,000
3. Research & Development Contracts				
a. 11 new contracts in 1976 converted to continuations in 1977.	---	11,291,000	---	+1,050,000
b. 34 new contracts in 1977	---	1,050,000	---	+3,600,000

4. Intramural Laboratory and Clinical Research				
a. Expansion of research related to influenza, hepatitis, DNA recombinants, and vaccine development in 1977	---	25,320,000	---	+1,325,000
Subtotal				+50,311,000
Total, increases				+50,986,000
Decreases:				
A. Built-in:				
1. One day less pay in 1977	---	13,565,000	---	-52,000
2. Nonrecurring costs-large equipment and renovations	---	900,000	---	-237,000
Subtotal				-289,000
B. Program:				
1. Research Grants				
a. 449 noncompeting awards in 1976 terminated or converted to competing in 1977 - regular program	---	57,417,000	---	-22,271,000
b. 41 new and 100 competing renewal awards in 1976 - regular program	---	12,139,000	---	-12,139,000
c. 2 noncompeting awards terminated in 1977 - special program, research career	---	2,265,000	---	-41,000
2. Training Programs				
a. 53 noncompeting fellowship awards in 1976 terminated in 1977	---	2,593,000	---	-1,423,000
b. 145 new fellowship awards in 1976	---	1,818,000	---	-1,818,000
c. 28 noncompeting training grants in 1976 terminated in 1977	---	3,523,000	---	-1,523,000
3. Research & Development Contracts				
a. 21 continuation contracts in 1976 terminated in 1977	---	11,291,000	---	-1,980,000
b. 11 new contracts in 1976	---	1,050,000	---	-1,050,000
4. Intramural Research and Direct Operations	611	---	-34	---
Subtotal			-34	-42,245,000
Total, decreases			-34	-42,534,000
Total, net change			-34	+8,452,000

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Obligations by Activity

Page Ref.		1976 Revised Pres. Budget Pos.	1976 Revised Pres. Budget Amount	1976 Appropriation Pos.	1976 Appropriation Amount	1977 Estimate Pos.	1977 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
231	Allergic and Immunologic Diseases.	---	$32,033,000	---	$33,345,000	---	$36,061,000	---	$+2,716,000
233	Infectious Diseases. . . .	---	56,116,000	---	61,386,000	---	65,411,000	---	+4,025,000
236	Intramural Research and Direct Operations	577	30,743,000	611	31,872,000	577	33,470,000	-34	+1,598,000
237	Program Management	10	244,000	10	249,000	10	271,000	---	+22,000
	Standard Level User Charge.	---	311,000	---	311,000	---	402,000	---	+91,000
	Total obligations. . .	587	119,447,000	621	127,163,000	587	135,615,000	-34	+8,452,000

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions.	621	587	-34
Full-time equivalent of all other positions.	60	67	+7
Average number of all employees.	676	649	-27
Personnel compensation:			
Permanent positions.	$10,689,000	$10,885,000	$+196,000
Positions other than permanent	473,000	491,000	+18,000
Other personnel compensation	487,000	506,000	+19,000
Subtotal, personnel compensation .	11,649,000	11,882,000	+233,000
Personnel benefits	1,916,000	2,021,000	+105,000
Travel and transportation of persons	420,000	480,000	+60,000
Transportation of things	100,000	107,000	+7,000
Rent, communications and utilities	520,000	560,000	+40,000
Printing and reproduction.	200,000	232,000	+32,000
Other services	4,554,000	5,181,000	+627,000
Payment to NIH Mgmt. Fund.	9,876,000	9,968,000	+92,000
Project contracts.	12,341,000	13,961,000	+1,620,000
Supplies and materials	2,675,000	2,961,000	+286,000
Equipment.	521,000	750,000	+229,000
Grants, subsidies and contributions.	82,390,000	87,511,000	+5,121,000
Insurance claims and indemnities	1,000	1,000	---
Total obligations by object	127,163,000	135,615,000	+8,452,000

Significant Items in House and Senate
Appropriations Committee Report

Item	Action taken or to be taken
1976 Senate Report	
1. The Committee expects the Institute to develop additional research centers for comprehensive attacks on these diseases (V.D.) and to stimulate the recruitment and development of young research talent for this important area of public health. (page 50 of Senate Report)	1. Funding for this area rose from $3,000,000 in FY 75 to over $4,000,000 in FY 76. A third center was established and a fourth will be awarded soon. Twenty-nine scientists are being trained under the support of NIAID grants and fellowships.

Authorizing Legislation

Legislation	1977 Authorization	1977 Appropriation Request
Public Health Service Act		
Title III, Part A, Section 301--Research and investigation, in general.	Indefinite	
Title IV, Part D, Section 431--National Institute of Allergy and Infectious Diseases	Indefinite	$128,654,000 2/
Title IV, Part I, Section 472--National Research Service Award Act of 1974 . . .	1/	6,961,000 2/

1/ Authorization expired June 30, 1975; extension legislation is pending.

2/ Funding estimate only.

National Institute of Allergy and Infectious Diseases
(Comparable)

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
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	109,022,000	127,163,000	127,163,000	
Items not considered		(7,934,000)	(7,934,000)	
1977	135,615,000			

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 as authorized by P.L. 93-192.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

NOTE: The figures presented in this table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of General Research Support Grants is no longer the function of this Institute. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes.

National Institute of Allergy and Infectious Diseases
(Actual)

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
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	126,852,000	126,852,000	
Items not considered		(7,934,000)	(7,934,000)	
1977	135,615,000			

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 as authorized by P.L. 93-192.

3/ Excludes R&D contracts not considered by House due to lacking authorization.

Justification

National Institute of Allergy and Infectious Diseases

	1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Allergic and immunologic diseases.	$32,033,000	$33,345,000	$36,061,000	$+2,716,000
Infectious diseases. . .	56,116,000	61,386,000	65,411,000	+4,025,000
Intramural research and direct operations . . .	31,054,000	32,183,000	33,872,000	+1,689,000
Positions . .	577	611	577	-34
Program management . . .	244,000	249,000	271,000	+22,000
Positions . .	10	10	10	--
Total, obligations.	119,447,000	127,163,000	135,615,000	+8,452,000
Total, positions. .	587	621	587	-34

General Statement

The National Institute of Allergy and Infectious Diseases has the mission of research on: (1) the immune system and its disorders, such as asthma, other allergies, chronic glomerulonephritis, certain forms of arthritis, and lupus erythematosis, as well as the manipulation of the immune system for successful organ transplantation and the treatment of diseases caused by immune system disorders; (2) all types of infection involving all body systems. This includes discovery and definition of new viruses, vaccine development, antiviral substances development, antimicrobial and antifungal therapy and new diagnostic methodology; and (3) a third important area concerns the potential usefulness of laboratory-created microbes.

NIAID conducts its mission through both extramural programs and intramural research. Investigator initiated research is encouraged through grants in areas where new knowledge is needed. Contracts are utilized for reagent development, for production and testing of new vaccines, and for other developmental activities. Intramural research encompasses development of new vaccine technology for diseases such as influenza and hepatitis and research on those problems of the immune system and infection where sustained long-term effort is needed to obtain solutions. The funds for these activities are allocated to maintain a continuing flow of new knowledge and to expolit the technological applications of new information of potential medical use or health benefit.

Since viruses are the cause of more illness than any other infectious agent and since there is not yet a satisfactory treatment of virus infections, the Institute gives a high priority to this area. The evidence of recent years linking viral infection to chronic and degenerative diseases, often mediated through induced disorders of the immune system, has reinforced the need for research to find new ways to prevent or treat virus infection. The full understanding of the immune system which forms the body's primary defense mechanism and how it can be regulated is essential if new ways are to be found to treat and prevent these diseases.

	1976 Revised Pres. Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Asthma and allergic disease centers program. . .	--	$2,900,000	--	$2,900,000	--	$3,132,000	--	$+232,000
The immune system and its disorders.	--	28,640,000	--	29,540,000	--	31,720,000	--	+2,180,000
Total		31,540,000		32,440,000		34,852,000		+2,412,000
Budget Mechanism:								
Research grants:								
Regular:								
Noncompeting.	368	22,051,000	368	22,051,000	277	20,376,000	-91	-1,675,000
Competing	43	3,688,000	50	4,273,000	145	8,409,000	+95	+4,136,000
Special:								
Scientific evaluation . .	5	235,000	5	235,000	5	284,000	--	+49,000
International centers for medical research . .	--	---	--	---	--	---	--	---
Research career program .	52	1,359,000	52	1,359,000	55	1,493,000	+3	+134,000
Subtotal	468	27,333,000	475	27,918,000	482	30,562,000	+7	+2,644,000
Fellowships	46	1,037,000	104	1,764,000	147	2,049,000	+43	+285,000
Training grants	16	1,163,000	16	1,163,000	6	550,000	-10	-613,000
Research and development contracts.	26	2,500,000	26	2,500,000	30	2,900,000	+4	+400,000
Total. . .	556	32,033,000	621	33,345,000	665	36,061,000	+44	+2,716,000

Allergic & Immunologic Diseases

In the past five years advances in research have defined the immune system as an organ made up of the white blood cells, bone marrow, thymus, lymph nodes, spleen, and elements of the liver. This organ system is under genetic control and is the primary host defense mechanism against microbes, viruses, and other antigenic materials derived from the environment. When it is deranged it is the fundamental cause of asthma and other allergies, autoimmune diseases such as acute and chronic glomerulonephritis, rheumatic heart disease, certain types of arthritis, lupus erythematosis, and disorders of the central nervous system. Deficiences or derangements in the immune system are a consequence of genetic, medical or environmental factors, or result in ways still to be explained, from persistent microbial or viral infections. Medically induced immune system derangements are substantial problems; for example, in the use of powerful immunosuppressive drugs in cancer therapy, organ transplantation and the treatment of a number of chronic disabling diseases. These derangements have led to susceptibility to infection by bacteria and fungi which are normally not a major medical problem in hospital practice and cancer therapy.

The NIAID has long sponsored the research which has now delineated the immune system as one of the most important of the body. This research is the primary source of the immunologic tools employed by the other categorical institutes for solving problems in their areas of responsibility. Many of the needed tools are yet to be developed. Since the basic system is not dissectable into independent parts related exclusively to certain organs or disease entities, the NIAID will continue its overall research program in all its aspects.

The increase in funding will enable the Institute to increase its research related to the immunocellular and immunogenetic determinants of the allergic and immune diseases, and to the immuno-pathogenetic mechanisms involved in certain lung, kidney, and arthritic diseases. It will also enable the Institute to give more emphasis to research on the mucosal and cellular defense mechanisms involved in such diseases as influenza, viral hepatitis, acute gastroenteritis, and in a variety of sexually transmitted diseases such as herpes or mycoplasmal infections where the more conventional approaches to immunoprophylaxis have not been effective.

The Institute is the major source of histocompatibility typing sera initially developed for use in matching for kidney and other organ transplants. Demands on this serum bank have now been expanded for studies on the relationship between certain histocompatibility antigens and susceptibility to a variety of diseases such as juvenile arthritis, cystic fibrosis, cancer and diabetes. Expansion of this important work will increase demands for these sera and create additional demands to enlarge supplies.

The increase in funding will also be utilized to intensify research on asthma, a major allergic disease from which 9 million Americans suffer and which causes 33 million days of disability per year and 5 million days lost from work at an estimated annual cost of $187 million.

	1976 Revised Pres. Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Hepatitis		$1,925,000		$1,985,000		$2,213,000		$+228,000
Influenza and other respiratory infections		3,675,000		3,735,000		4,677,000		+942,000
Sexually transmitted diseases		3,084,000		4,084,000		6,134,000		+2,050,000
Nucleic acid recombinants		1,024,000		1,955,000		2,080,000		+125,000
Total		9,708,000		11,759,000		15,104,000		+3,345,000
Budget Mechanism:								
Research grants:								
Regular:								
Noncompeting	591	35,366,000	591	35,366,000	451	32,611,000	-140	-2,755,000
Competing	53	4,528,000	91	7,866,000	238	13,846,000	+147	+5,980,000
Special:								
Scientific evaluation	--	---	--	---	--	---	--	---
International centers for medical research	4	2,400,000	4	2,400,000	4	2,400,000	--	---
Research career program	35	906,000	35	906,000	40	1,131,000	+5	+225,000
Subtotal	683	43,200,000	721	46,538,000	733	49,988,000	+12	+3,450,000
Fellowships	70	1,556,000	157	2,647,000	213	2,912,000	+56	+265,000
Training grants	34	2,360,000	34	2,360,000	16	1,450,000	-18	-910,000
Research and development contracts	96	9,000,000	106	9,841,000	115	11,061,000	+9	+1,220,000
Total	883	56,116,000	1,018	61,386,000	1,077	65,411,000	+59	+4,025,000

Infectious Diseases:

Although medical science has moved infectious diseases from first to fourth place as a cause of death, infections are still the leading cause of illnesses responsible for days of bed disability, school and work absenteeism, and cost an estimated 10 billion dollars annually. Influenza, "the last of the great plagues," is a killer of older patients and those with underlying bronchopulmonary or heart disease. Sexually transmitted diseases are now the most common bacterial infection. Elimination of viral hepatitis B as a blood transfusion problem has done little to change the overall attack rate and a significant proportion of chronic liver disease results from these infections. Chronic pyelonephritis is an important cause of end-stage kidney disease requiring dialysis or transplantation. Chronic and persistent viral infections have been shown to cause degenerative diseases of the central nervous system and probably underlie a variety of other degenerative diseases including some forms of diabetes and other conditions which have been regarded as genetic or metabolic in origin. Because of the wide variety of infectious agents and of the disease spectrums they produce, the research program remains committed to finding new solutions to continuing problems.

The increased funding will enable the Institute to expand and intensify its research in several specific areas where new opportunities exist or which have recently become more important problem areas. Among these are:
Influenza: Recent development of attenuated influenza viruses - bearing genetic defects which can be transmitted into other influenza viruses by recombination and thereby attenuate the recipient virus - has opened new opportunities for the development of live influenza vaccines. One such attenuated strain has been developed in NIAID laboratories. Its well defined genetic markers of attenuation can be transmitted to other recipient strains which infect volunteers without causing illness. Since live vaccines administered intranasally stimulate both local respiratory tract and humoral immunity and since such vaccines can be produced more rapidly and economically than killed vaccines, the NIAID is moving as rapidly as possible towards determining the feasibility of using live vaccines by the time the pandemic is likely to occur -- the late 1970's or early 1980's. These efforts will involve production of vaccines as new strains occur in patients, the experimental immunization of large population groups to determine efficacy, and the development of the technologies for the new methods of administration. Acceleration of this work is vital to the early application of this capability for better immunization against influenza.

Viral Hepatitis: Emerging evidence indicates that hepatitis B virus is a major cause of non-blood transmitted hepatitis in the United States and may be responsible for more than half of the total number of cases. There is also now clear evidence that one or more still unidentified hepatitis viruses other than hepatitis A and B viruses exist, and can cause both blood induced and non-blood induced infections.

The NIAID has devoted major efforts to the development of a prototype hepatitis B vaccine which is now being tested in chimpanzees for safety and efficacy. There is need to begin testing in volunteers during the next year as the first step toward usage of such a vaccine in prevention of this form of hepatitis, and to place under surveillance the population groups in which the later efficacy trials will be carried out. Because of the probable role of the immune system in chronic hepatitis related to hepatitis B infection, special immunologic monitoring and long-term surveillance will be necessary in the recipients of the vaccine.

There will also be continuing efforts to cultivate the hepatitis viruses in in vitro cell systems and to provide new diagnostic methodologies for hepatitis A and non-A non-B hepatitis.

Sexually Transmitted Diseases: Gonorrhea and syphilis, the two most widely recognized of these diseases, continue as unsolved problems. More recently the importance of several other sexually transmitted diseases has been recognized as being in toto perhaps an even greater health problem than syphilis and gonorrhea. These diseases include genital herpes (Herpes type II, possibly associated with cancer of the cervix), chlamydia (small intracellular organisms), mycoplasmas (bacteria without cell walls cultivatable on laboratory media), trichomonas (a protozoan parasite), group B streptococci, and hepatitis B virus.

Herpes II infections are painful, disfiguring, persistent infections for which no good treatment exists. More over, there is danger of neonatal infection to babies born of women with this infection and it is estimated that perhaps as many as one in every 3,000 live births are infected. Neonatal infection may progress rapidly to death or result in retardation. Hepatitis B virus as a neonatal infection gives rise to a prolonged carrier state with liver damage in a high percentage of the infants infected. Such infants are hazardous to their contacts. High titered gamma globulin may be able to prevent neonatal infection but this is in need of evaluation.

The effort on gonorrhea and syphilis must be sustained, and new resources must be placed into the other diseases.

Biohazards: Heredity in all classes of living organisms is determined by the nucleic acids DNA and RNA. In the past few years publicized experiments have described the insertion of nucleic acids (DNA) or fragments of one species into the genetic apparatus - both chromosomal and extra-chromosomal - of cells of other species, to create new and unnatural hybrids. This ability for genetic manipulation has an awesome potential for good as well as harm. It was the recognition of the potential biohazard which spurred an international group of scientists to recommend a voluntary moratorium on such research until the situation could be publically examined and guidelines for safety developed.

The potential for benefit includes such possibilities as the production by bacteria of hormones (insulin and others), enzymes and antibodies of various types. This same technique may make possible the transfer to bacteria and to the important food grains, the ability that legumes and clover have to fix nitrogen. In the far distant future this research may lead the way to treat certain genetic diseases.

To perform these experiments safely requires the development and distribution to investigators of "vectors" (bacterial plasmids or phages) which enable insertion of the DNA into safe "hosts", such as bacterial cells modified to have a restricted capacity to escape from the laboratory and infect mammals. The NIH has assigned to the NIAID the responsibility for development and distribution (to the scientific community) of safer vectors and hosts. A related concern is that of hybrid or altered viruses which may acquire a capacity of inserting viral genetic material into the genes of the host and cause disease by transformation or by abnormal immune response. While many naturally occurring viruses relating to cancer or other chronic diseases have this capacity, still others may result from laboratory research.

This research on recombinant DNA represents a new initiative which will require additional funds.

Viral Gastroenteritis: Several new viruses have been identified which cause acute nausea, vomiting and/or diarrhea. One of these causes a severe diarrhea in children under the age of 2, and is worldwide in its distribution and is a frequent cause of death in malnourished or otherwise compromised children. NIAID scientists succeeded in growing this virus in tissue culture in 1975 and believe a vaccine can be made. This work will be expanded.

Intramural Research and Direct Operations

	1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Intramural laboratory and clinical research.	$24,706,000	$25,320,000	$26,923,000	$+1,603,000
Positions. .	470	495	470	-25
Other direct operations . .	6,348,000	6,863,000	6,949,000	+86,000
Positions. .	107	116	107	-9
Total, obligations.	31,054,000	32,183,000	33,872,000	+1,689,000
Total, positions. .	577	611	577	-34

Scientists in intramural laboratories are engaged in a wide variety of virological, microbiological, immunological and clinical research related to the immune system, asthma, allergy and other immune disorders, to infectious and parasitic diseases, and to antivirals. This research is multidisciplinary and requires sustained full-time effort.

Other Institute staff, working with consultants and advisory groups, develop and administer programs to be carried out under grant or contract projects. Grant projects are investigator initiated, but may fall into one of several areas singled out for special emphasis. Over 2,000 applications will be processed this year. Contracts normally result from the need to transfer certain basic findings, developed either under grant or by intramural scientists, into practical application. Institute staff serve as project officers and assure collaboration with NIAID funded projects. This view of science as a continuum of activity from basic research finding to public benefit is essential to Institute policy.

Intramural scientists are also the core of NIAID developmental efforts for vaccines against acute respiratory diseases, hepatitis and viral gastroenteritis. New candidate vaccines are developed in NIAID laboratories and tested in volunteers in its Clinical Center or in contractor facilities.

The additional funding will expand opportunity for progress in these efforts at vaccine development. Emphasis is being given to influenza in view of an expected pandemic in the next 5 years, and there is a need to increase the number of volunteers and trial centers to test and validate the strains which will be produced for larger scale field trials. For smaller scale efficacy trials, additional lots of vaccines will have to be produced and safety tested. The number of volunteers available for these studies is a limiting factor on the rate of progress and additional facilities for trials will be developed. The prototype hepatitis B vaccine will also have to be prepared, packaged, and tested for sterility and antigenicity in animals before it is given to volunteers. Since it is necessary to use the same lot of vaccine in the later efficacy trials as that tested initially in volunteers, this requires that all vaccine be prepared before beginning the initial studies.

Intramural scientists will also play a vital role in research on the biohazards of nucleic acid (DNA) recombinants. This will require renovations and special equipment to meet the new NIH guidelines for research in this area and will increase the demands for supplies and animals.

The development of the intramural Clinical Asthma and Allergy Center has led to growth of outpatient needs. Since these cannot be met at the NIH until the Clinical Center is enlarged, there is need to develop collaborative arrangements with nearby medical centers with additional costs involved.

Also included in this activity are funds for the Institute's portion of centrally furnished services such as maintenance, security and patient care.

The overall increase of $1,689,000 for Intramural Research and Direct Operations represents $364,000 for mandatory items and $1,325,000 for program expansion as described above.

Program Management

	1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Program management. .	$244,000	$249,000	$271,000	$+22,000
Positions . .	10	10	10	--

This activity contains funds and positions required to provide overall direction and management for the Institute.

A new Director and Deputy Director were appointed late in FY 1975. Most of their activities for the coming year will be directed toward an evaluation of the on-going activities with the intent of ensuring that resources are allocated to those areas with the highest potential for pay-off. The Institute will continue to be deeply involved with preventive medicine, with particular emphasis on vaccine development, and an understanding of the immune system.

Following a complete review of current opportunities and efforts, a restructuring of the organization will be undertaken. Underlying any reorganization will be the desire to bring together in a program area all activities relating to a particular class of diseases (e.g., infectious) without concern for whether the work done is through grant, contract, or intramural research.

Since the immune system and its disorders play a major role in most of the major diseases, it is of vital importance that the Institute maintain liaison with the other Institutes to avoid duplication and guarantee rapid dissemination of results. In addition, Program Management Staff serve on government-wide committees on hepatitis, influenza and sexually transmitted diseases.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Allergic and Immunologic Diseases (PHS Act, Title IV, Parts D and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$33,345,000	Indefinite	---	$36,061,000

Purpose: This program conducts and supports research and research training on a wide variety of diseases attributable to deficiencies or disorders in the responses of the body's complicated immune mechanisms, including allergies.

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 1976: The 16 Asthma and Allergic Disease Centers continue to make research advances that have direct clinical significance for patients including: more specific material for diagnosing insect sting allergies, improved inhalation tests for asthma diagnosis and monitoring, superior desensitizing antigens, and improved drug treatment.

All patients required for the 2 year long evaluation of the usefulness of antilymphocyte globulin in transplantation have now been acquired and entered in the study.

Research support under this activity included about 475 research grants at an average cost of $59,000 and 120 training and fellowship awards for $2,927,000 and 26 contracts at an average cost of $96,000.

Objectives for FY 1977: An Investigational New Drug application will be filed for the 3 purified antigens of ragweed. This will make these products of the contracts program available for more widespread clinical evaluation.

A new Manual for Tissue Typing Techniques will be published early in the year. Techniques for better definition and typing of leukocyte defined (LD) antigens should lead to a better understanding of these important antigens. Every effort will be made to continue funding the highest quality fundamental and developmental studies of the immune response system. These studies are not only relevant to understanding the ways in which the body is protected; but also the mechanisms by which many diseases, such as cancer, heart and kidney disease, are produced.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Infectious Diseases (PHS Act, Title IV, Parts D and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$61,386,000	Indefinite	---	$65,411,000

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 parasites, 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 1976: Venereal disease research was significantly increased by the funding of 2 additional centers that permit the maintaining of multi-disciplinary research efforts together with ready access to clinical patients.

Noteworthy in influenza research were the efforts to develop and test a range of temperature mutant vaccine strains and to predict their relative degree of attenuation.

Hepatitis research has shown that in addition to the well recognized and now specifically diagnosable hepatitis type A & B, there exists a considerable amount of disease that must be due to a third agent(s).

Objectives for 1977: In venereal diseases there will be continuing emphasis on the sero typing, antigenic structure and mechanisms of venereal disease production. Work on the nongonorrheal - nontreponemal forms of disease will be expanded.

Preliminary trials of hepatitis B vaccine in humans will start despite a somewhat delayed schedule in 1976.

Agreement on the potential hazards of nucleic acid recombinant research and the limited availability of safer hosts and vectors for genetic material should permit acceleration of this field of research which has large ultimate potential for practical benefits in medicine and agriculture.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Intramural Research and Direct Operations (PHS Act, Title IV, Part D)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
611	$32,183,000	Indefinite	577	$33,872,000

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. The program also provides for the overall coordination and administration of the Institute's grants and contracts program and services rendered by the National Institutes of Health.

Explanation: Program scientists and managers interact in a consultative, advisory and cooperative fashion with members of other institutes and government agencies, as well as with private practitioners and academic researchers.

Accomplishments in 1976: The active cooperation of intramural scientists in the Collaborative (contracts) Research Program continues unabated, especially in influenza and hepatitis research. The causative viruses of human gastroenteritis were further characterized and a specific serological test for one of these was developed. The ultimate explanation of the role of viruses in the causation of cancer was brought a step closer by the proof that a part of the normal genetic material in mice with high incidence of leukemia includes the complete genome of mouse leukemia virus.

The general assumption that immunologic mechanisms can cause a variety of diseases was further strengthened by the finding that the glomeruli of human kidneys can contain a receptor for C3b, a specific component of the blood substance called complement. In glomerulonephritis, the most common renal disease, it has been known that aggregates of antigen, antibody and complement clog the filtering apparatus (glomeruli) of the kidney. It now seems probable that this is not non-specific clogging of a molecular sieve but a highly specific mechanism of attachment.

Objectives for 1977: To continue program with increased emphasis on better diagnosis and correction of immune disorders, virus diseases (including antivirals and vaccines) and the ways in which bacterial and viral genetic material interchanges and interacts with that of a host.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Program Purpose and Accomplishments

Activity: Program Management (PHS Act, Title IV, Part D)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
10	$249,000	Indefinite	10	$271,000

Purpose: This program provides over-all coordination and direction for Institute activities. Included are personnel costs and direct operations for the Director and his immediate staff.

Explanation: The majority of the funds are for personnel compensation, with a small amount provided for operating costs.

Accomplishments in 1976: A new Director was appointed and much of the year was spent reviewing current activities. The position of Deputy Director was created to assist the Director in running the day-to-day operations and allow him more time to concentrate on direction of the national effort. A new Scientific Memorandum on nucleic acid recombinants was distributed.

Objectives for 1977: Primary among the objectives for 1977 will be the implementation of the reorganization begun in 1976. Program Management staff will be involved in deciding on allocations of funds, manpower, and material to the various areas. A thorough review of the Institute's international programs will be undertaken. Liaison with other research institutes and governmental agencies at Bethesda and elsewhere will be a major activity. Expanded programs of research on sexually transmitted diseases will be developed. Contract review and approval procedures will be revised to ensure more discussion of program relevancy and priority early in the process.

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Estimate	Transition Quarter
Allergic and immunologic diseases.	$33,345,000	$7,003,000
Infectious diseases.	61,386,000	12,254,000
Intramural research and direct operations.	32,183,000	7,787,000
Program management	249,000	60,000
Total.	127,163,000	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 accounting data for the first quarter of FY 1976.

THURSDAY, FEBRUARY 26, 1976.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

WITNESSES

DR. RUTH L. KIRSCHSTEIN, DIRECTOR
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. RONALD W. LAMONT-HAVERS, DEPUTY DIRECTOR, 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
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

AFTERNOON SESSION

Mr. NATCHER. We will now continue the National Institutes of Health with the National Institute of General Medical Sciences. The presentation will be made, of course, by Dr. Ruth L. Kirschstein, the Director, and we have a biographical of you, Dr. Kirschstein, which we will place in the record at this point.

Name: Ruth L. Kirschstein.

Position: Director, National Institute of General Medical Sciences.

Birthplace and date: Brooklyn, N.Y., October 12, 1926.

Education: A.B., magna cum laude, 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; Intership, 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.

Special awards or 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.

DHEW Superior Service Award, 1971.

Member, Board of Consultants, Journal of Medical Primatology.

Member, Primate Research Center Advisory Committee, Division of Research Resources, NIH.

Member, National Commission on Diabetes.

Member, National Commission on Arthritis and Related Musculoskeletal Diseases.

Member, *Ad Hoc* Committee on Reserpine and Breast Cancer.

Chairperson, NIH Grants Peer Review Study Team.

Member, Editorial Board, Journal of Toxicology and Environmental Health.

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 new-born 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.

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Kirschstein, 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).

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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.: Cyclamates. *Human Pathology*, 5:498, July 1974.

Kirschstein, R. L.: Toxicology and carcinogenicity of preservatives used in the preparation of biological products. International Symposium on Preservatives in Biological Products, San Francisco, 1973. *Develop. Biol. Standard*, 24:203–212, 1974.

Hoel, D. G., Gaylor, D. W., Kirschstein, R. L., Saffiotti, U., and Schneiderman, M. A.: Estimation of risks of irreversible delayed toxicity. *J. of Tox. and Environ. Health*, 1:133–151, 1975.

Mr. NATCHER. I see you have a prepared statement. How do you want to handle this?

Dr. KIRSCHSTEIN. I think, sir, I will touch the highlights of it, if I may.

Mr. NATCHER. Without objection, we will insert your full statement in the record.

Dr. KIRSCHSTEIN. Yes, sir.

[The statement follows:]

Mr. Chairman, members of the committee: I have the honor of appearing before you for the second time. I should like to present to you the programs of the National Institute of General Medical Sciences and indicate to you how these broad, basic scientific endeavors undergrid and support the programs of

those institutes whose missions are specifically disease-oriented. Without support for the basic biomedical and clinical research programs of the NIGMS, the understanding and prevention of human disease and development of treatment will be slowed.

CELLULAR AND MOLECULAR BASIS OF DISEASE PROGRAM

The largest program area upon which research activity of this Institute is focused is the cellular and molecular basis of disease program. Millions of microscopic, specialized cells functioning in unison constitute each of the several tissue components of an organ, such as a kidney or the liver. Thus, in the embryonic development of organs, cells must accumulate and adhere to form the organ tissues. Growth of organs and the body as a whole occurs by constant multiplication of these cells. Since the cell is the basic structural and functional unit of all living systems, manifestations of disease must be described ultimately in terms of differences from the normal structure and function of cells and conglomerates of cells, namely, tissues and organs. Each individual cell has a surface which is a complex membrane consisting of combinations of sugars or carbohydrates, proteins and fats—lipids—which are unique for each tissue.

It has been known for many years that the body recognizes and reacts to cells or tissues which are "foreign" to it. But, how do cells of the body's own tissues recognize each other? What holds such cells together in a characteristic recognizable and functional structure? Why do cancer cells lose these normal properties?

To answer these questions, NIGMS grantee Dr. Luis Glaser and his associates at Washington University School of Medicine in St. Louis have performed a series of elegant experiments on membranes from embryonic chick retina cells.

If cells from a specific tissue, such as the retina of the eye, are separated in a nutrient solution, they begin to aggregate again and eventually reproduce many features of the original tissue. Furthermore, if cells from two different tissues, such as brain and retina, are mixed, they soon begin to sort out into two different, entirely separate aggregates—one of brain cells and the other of retina cells. Scientists believe that this ability of like cells to recognize and specifically attach to each other is due to molecules found on their surfaces. These are called cell-surface recognition sites. Dr. Glaser and his coworkers demonstrated that these recognition sites were, indeed, present on isolated membranes.

The next question to be answered concerned specificity: Were the cell-surface recognition sites on the isolated membranes specific, that is, capable of recognizing only the same cell type? Dr. Glaser performed another series of experiments in which he mixed the isolated retina cell membranes with whole retina cells in one vessel and with whole brain cells in another. In the first test the retina cell membranes readily became attached to the retina cells; but in the second test, retina membranes did not bind to the brain cells, thus showing specificity. These NIGMS investigators are now attempting to isolate cell-surface recognition site material from the retinal membranes in order to determine its chemical composition and structure. It is hoped that the study of these recognition molecules of normal tissues will elucidate the changes that almost certainly occur in cancerous tissues.

GENETICS PROGRAM

Another basic program which is supported by the NIGMS is in genetics, in which development of knowledge concerning the inheritance of disease states is fostered. Such support includes efforts at understanding the structure and function of the basic genetic materials of cells, the chromosomes, and the genes.

There is currently much concern about chromosome damage caused by a number of environmental agents, such as pollutants, industrial chemicals, and drugs. The effects of such damage may be seen directly in the exposed individual, resulting in an increased probability of developing cancer or, alternatively, the effects may extend over several generations because of heritable defects not initially apparent.

Chromosome breaks occur regularly as a result of wear and tear on the cell. Their incidence may be increased by exposure to hazardous agents. These breaks can be repaired by special enzyme systems which rejoin broken strands of DNA in the chromosomes. Since the DNA strands in each chromosome are paired, this repair process may result in an exchange of material between op-

posite strands of a DNA pair, the "sister-chromatids," which can be seen during the process of cell division or mitosis. A technique recently developed by an NIGMS grantee permits detection of sister chromatid exchanges, and is therefore an indicator of possible genetic damage in human chromosomes. Such exchanges are relatively frequent, compared to permanent chromosome breaks. Agents previously examined for their ability to cause permanent chormosome changes can now be reexamined by this sensitive technique.

Furthermore, it has been shown that, in certain hereditary diseases in which an increased chromosome fragility occurs, there is a greatly increased risk of development of cancer; and the tests described here may, therefore, be adaptable as screening methods for malignancy. This cytogenetic methodology, developed by an NIGMS grantee, has thus had importance in the understanding of and ability to detect cancers and cancer-causing chemicals. Indeed, it is not uncommon to find that the most basic scientific endeavors will, in the most unexpected way, have a very specific impact in advancing our knowledge of the cause, cure, or prevention of specific disease entities.

CLINICAL AND PHYSIOLOGICAL SCIENCE PROGRAM

As you know, one of the major clinical research endeavors supported by NIGMS concerns research into burn injuries. It has been known for many years that the amount of energy expended by patients with severe body burns is approximately twice that of normal individuals. At the same time, these severely injured patients are often unable to obtain sufficient nutrients by mouth to satisfy their energy requirements. Therefore the patient is forced to consume his own tissue as a fuel source to support his vital functions. During the past 4 years, a team of investigators at the University of Washington Burn Research Center, under the direction of Dr. William Cureri, has been able to prevent this life-threatening metabolic imbalance in over 500 patients, by developing a precise formula which predicts the caloric requirements of patients based on body weight and percent of the body surface burned. They then combined intravenous administration of very concentrated sugar and protein solutions with the constant delivery of nutrients into the stomach via a nasogastric tube. This technique has made it possible to prevent weight loss in these patients throughout their entire hospitalization, whereas prior to the development of these extraordinary feeding techniques, patients with greater than 40 percent burns regularly exhibited weight loss of 25 percent of their body weight during the first 8 weeks in the hospital. It must be emphasized that an acute loss of 30-percent body weight is usually associated with death. Life-threatening starvation in acutely burned patients can develop insidiously and is often not recognized. Up to 60 percent of energy expenditure in a bedridden patient is required just for normal breathing. The usual mode of death in these patients is progressive pneumonia. Institution of these extraordinary nutritional programs has maintained patients in energy balance, with not only maintenance of body weight, but also more rapid wound healing, better acceptance of skin grafts, and, finally, improved cellular function. These techniques have allowed an increase in the survival of these patients. The investigators at University of Washington have been able to achieve a better than 50-percent survival in young, adult patients with 85-percent total body-surface burns. This figure represents a significant improvement. Prior to the introduction of such improved dietary programs the mortality rate was 100 percent.

Last year I told you of the progress made at the Burn Research Center at the Massachusetts General Hospital in Boston in defining the steps needed to successfully treat persons with 80 percent or more of the total body surface burned. One of those steps involved early transplantation of skin grafts. A satisfactory synthetic replacement for skin has been sought for many years; but, until recently, there has been no success. A preliminary report to us from this group, which you may have read in the December 30 issue of the Washington Star discussed the development of "artificial skin from animal tissues." This "artificial skin" is a composite of carbohydrates—starches and sugars—and protein fibers derived from cattle. These fibers are then coated with a second biologic material which protects them from being dissolved by the naturally occurring enzymes of the human body. The fiber reinforcement makes the material strong; and when it is in place, covering a burned area, it prevents fluid loss and infection, two of the most serious complications of severe burns. Thus far, in animal experiments, this material does not produce inflammation or irritation and has not been rejected, as real skin is, allowing healing to take place without secondary complications.

This endeavor was a cooperative effort between Dr. John Burke, director of the Burn Research Center at the Massachusetts General Hospital and biomedical engineers at the Massachusetts Institute of Technology, using the principles of materials development learned in space technology. This is an example of collaboration between two of the NIGMS program emphasis areas, burn research and biomedical engineering.

BIOMEDICAL ENGINEERING PROGRAM

The development of useful biomaterials is an important part of the NIGMS biomedical engineering program. These biomaterials are substances which can be used as replacement materials within the body and to which little or no reaction or rejection occurs. A new biomaterials combination involves the use of a "bioglass" coating on aluminum oxide ceramic joints. Bioglass is a specially designed glass which has the unique property of forming a chemical bond with bone that is as strong as the bone tissue itself. Therefore, repair parts coated with bioglass and implanted in bone or as a replacement joint do not become loose with time. In order to eliminate problems of wear, the joints are made of very high-strength aluminum oxide ceramic which is so hard that the mating surfaces show almost no wear. By coating the ceramic parts with bioglass using specially developed procedures the problems of wear and tear currently encountered in joint replacement may be eliminated. An NIGMS grantee, Dr. Larry Hench at the University of Florida, has developed these new joint replacement materials and is currently performing tests of bioglass-coated ceramic hip joints in sheep. These show considerable promise. Tests of the bioglass coating on stainless steel hip joints in monkeys also show development of a very strong bond with bone. Long-term animal tests of 2–5 years will be necessary to establish usefulness, but the prospects are bright.

PHARMACOLOGY-TOXICOLOGY PROGRAM

The pharmacology-toxicology program of the NIGMS, in addition to studying the beneficial therapeutic effects of drugs, is concerned with the toxicities caused by such drugs and with the development of animal models for the study of drug-induced diseases. An NIGMS grantee at the University of Iowa toxicology center has been studying the morphological and biochemical effects of the administration of large doses of an antihistaminic drug, cyproheptadine, to rats. Cyproheptadine has been found to cause a specific and unique type of pancreatic toxicity in rats. The pancreas, as you know, is the site of insulin production in the body. When given orally over a period of 14 days in very large doses, cyproheptadine causes damage to the pancreas and induces diabetes in rats. These changes are reversible and are different than the toxic effects of other drugs which have been shown to induce diabetes in rats. The biochemical and metabolic changes that occur as a result of the administration of this drug are a marked reduction in insulin in the pancreas and a high level of glucose or sugar in the blood. However, the blood level of insulin is not lowered, a fact not yet understood by indicating a different and, for the first time, reversible type of drug-induced diabetes. This work may provide a model for the elucidation of this important disease in which the Congress has taken interest and has enacted special legislation. The NIGMS, through its continued support of programs in basic and clinical research related to fundamental knowledge of the body's functions, hopes to contribute to the understanding of diseases such as diabetes.

Mr. Chairman, in order to support programs such as those described above, the budget request for the National Institute of General Medical Sciences for 1977 is $193,435,000. I shall be pleased to try to answer any questions and supply any additional information desired for the record.

Mr. NATCHER. All right, Doctor, go right ahead.

Dr. KIRSCHSTEIN. Yes, sir, Mr. Chairman.

I would like to present to you the highlights of the program of the National Institute of General Medical Sciences and indicate to you how these broad basic scientific endeavors undergird and support the activities of other Institutes whose missions are specifically disease oriented.

CELLULAR AND MOLECULAR BASIS OF DISEASE

In our largest program area, cellular and molecular basis of disease, studies means by which cells of the body's tissues recognize each other and form functional structures or organs.

These scientists have shown that the surfaces of cells have sites for the specific recognition of cells from similar tissues and not from cells of other tissues.

They are now attempting to isolate these cell surface recognition sites in order to determine their chemical composition and to study how these recognition molecules may elucidate changes in diseased tissues, particularly cancerous tissues.

GENETICS

In our genetics program, about which you heard some mention this morning from Dr. Krause, in relation to geinetic engineering, in addition to efforts in that direction, grantees are studying inheritance and the basic genetic components, chromosomes and genes. In certain disease states, and as a result of numerous environmental agents such as pollutants, industrial chemicals and drugs, chromosome changes and chromosome damage occur.

This damage can now be studied by a technique which was developed by an NIGMS grantee, in which the ability of a specific dye to stain chromosomes is used to measure the degree of chromosome breakage and repair. This method turns out to be an extremely sensitive one and may be used as a measure of the toxicity of many chemicals and, since chromosome damage is often a precursor of cancer, it may indeed be a screening method for malignancy.

TRAUMA AND BURN RESEARCH

In addition to programs in these basic scientific areas, the NIGMS supports certain clinical endeavors, particularly research into burn injuries.

One of the major problems in severely burned patients is the maintenance of nutrition. Burn patients may have to, if they are not provided with sufficient nutrition, consume their own tissues for fuel to support their vital functions.

One of our grantees, Dr. William Curreri, at the University of Washington, has developed a precise formula that can predict the caloric requirements of such patients, and by the combined use of intravenous administration of concentrated sugar and protein solutions and the delivery of nutrients by nasogastric tube, he has been able to prevent weight loss and, in some cases, death in these patients.

For years scientists who are involved in burn research have been looking for a means of developing an artificial skin to substitute for skin to use in grafting. A very preliminary observation from one of our grantees at the Massachusetts General Hospital, which was actually reported in the Washington Star on December 30, has indicated the possible development of an artificial skin from carbohydrate material and protein fibers derived from cattle. These fibers are very, very

strong and can be put in place to cover burn surfaces, preventing fluid loss, and secondary complications such as infection. In animal tests performed to date it does not look like this so-called artificial skin will be rejected. This is in a very preliminary stage and more work is needed. The study was carried out in conjunction with biomedical engineers, and is another example of how a biomaterial is being developed.

BIOMEDICAL ENGINEERING

In our biomedical engineering program, another biomaterial called bioglass is being developed which has the unique property of forming a chemical bond with bone, that is as strong as the bone tissue itself. At present, long-term animal tests are being carried out to see whether this material, when bonded with bone, can be used as a replacement for joints such as hip joints.

PHARMACOLOGY-TOXICOLOGY

Finally, a grantee in our pharmacology-toxicology program is studying the toxic effects of numerous drugs, including an antihistaminic drug called cyproheptadine. One of our grantees has found that oral administration of large doses of this drug causes a specific and unique, reversible toxic change in the pancreas of rats, leading to the development of diabetes, a disease in which the Congress and this committee has taken a great interest.

The NIGMS hopes through this research to develop an animal model for further work on diabetes and, with this program, as with all its others in basic research, hopes to be able to contribute to the elucidation of many diseases, including diabetes.

For this, Mr. Chairman, we have asked for support in our budget request for the year 1977, of $193,435,000.

I would be pleased to answer any questions.

1977 BUDGET INCREASE

Mr. NATCHER. Thank you very much, Doctor.

Now, Doctor, your budget for 1977 proposes an increase of $6 million. How do you plan to use the additional amount?

Dr. KIRSCHSTEIN. Mr. Chairman, this is an increase of $6 million, but in point of fact, with the commitments on the books for research grants and the increased costs per year of research, the extra money will not allow us to engage in very much new activity.

Mr. NATCHER. In your opening statement to the committee you mentioned the concern about chromosome damage caused by a number of environmental agents. Are you supporting research on the effects of specific drugs or chemicals?

Dr. KIRSCHSTEIN. Mr. Chairman, our research is in support of very basic studies. Our Institute is known as the Institute that supports the most basic endeavours in the scientific arena. Usually when these studies become more focused on particular drugs that are used in specific disease entities, or on environmental agents, the work is picked up by the other categorical Institutes.

Mr. NATCHER. When one of our scientists identifies a particular pollutant or industrial chemical that causes chromosome damage, what

do you do with this information? Do you call it to the specific attention of EPA, the National Institute of Occupational Safety and Health, the National Institute of Environmental Health Sciences, or just what do you do, Doctor?

Dr. KIRSCHSTEIN. That is exactly what we do. We call it to the attention of the appropriate organization either an Institute of the National Institute of Health or another agency within the health establishment or within other parts of the Government.

In addition, when, in the course of studies in our pharmacology-toxicology program, drugs are determined to cause certain problems, we inform the Food and Drug Administration. As in the case of the drug that I talked about, in my opening remarks, the antihistaminic drug, cyproheptadine, we informed the Food and Drug Administration of the findings so that reevaluation can be done of the drug for human use.

CHROMOSOME CHANGES

Mr. NATCHER. You also mention in your statement that one of your grantees recently developed a technique which permits detection of chromosome changes.

Can you describe the technique to the committee, and tell us if it is expensive, if it is time consuming, just what position that it is in?

Dr. KIRSCHSTEIN. Mr. Chairman, this grantee was performing very basic studies and in the course of these, he discovered a technique to determine how chromosomes are damaged and how they break and then are repaired. During this process there may well be an exchange of the strands of the chromosome, a so-called sister-chromatid exchange. When this happens, the specific dye that these chromosome strands usually take up, is inhibited from being taken up, and there is a lack of staining. An exchange of sister-chromatids can then be shown by the fact that there is a lack of staining indicating that previous damage and then repair had occurred.

The technique seems very, very sensitive. Our grantee and others are currently working in an attempt to make this a test which can then be used widely. It is not quite that far along.

Mr. NATCHER. Doctor, as you know, the National Institute of Environmental Health Sciences has been working on a quick test to identify carcinogenic agents. Could this be the same kind of a test?

Dr. KIRSCHSTEIN. No; this is not the same test as that. That is a test of mutagenesis that is performed on bacteria, and is related to whether or not certain bacterial mutants, or different strains of bacteria, will react in certain ways to certain chemicals. Our chromosome study would more likely be a test of the same types of chemicals but performed in cultures of animal cells. So these are two projected activities going along somewhat the same line but, very possibly, in different directions.

Mr. NATCHER. You have also said that this technique can be used to reexamine previously tested agents. Will this technique be used by the Cancer Institute at its Frederick Research Center, as well as the National Institute of Environmental Health Sciences, or will it be simply the property of the grantee?

Dr. KIRSCHSTEIN. No, sir; the grantee has already published this finding in a very widely read journal, the "Proceedings of the Na-

tional Academy of Sciences," and we and others will take the responsibility, and have already done so, of informing scientists who work in other areas and scientists in the National Cancer Institute and the National Institute of Environmental Health Sciences about the possibilities of this technique so they may try to develop it in such a way that it can be used on wide screening basis.

Mr. NATCHER. Now, Doctor, how will the DNA Advisory Panel's suggested guidelines affect your grant supported research, if any?

Dr. KIRSCHSTEIN. It will affect it very substantially. Our genetics program along with the National Institute of Allergy and Infectious Diseases supports probably the largest portion of research that is related to DNA and to the possibility of using recombinant molecules.

Indeed, it was grantees from our Institute who were among the first scientists that put together the suggestion for the moratorium, and began this long process that we have been talking about.

We have recently sent to all our grantees, in this area, I believe some 480 of them, a letter which has asked them to inform us of what areas of research they have even under consideration in this regard, in hopes of determining what work they either had contemplated doing, what work they had stopped because of the moratorium and what work they are planning for in the future, and what help they might need, when the guidelines finally come out.

Mr. NATCHER. Can you give us some idea as to when the guidelines will be officially imposed?

Dr. KIRSCHSTEIN. As a result of a series of meetings, the first one of which was held in California about a year ago, a series of preliminary guidelines have been developed, as Dr. Fredrickson and others told you this morning.

These have now been reviewed, and considered by many people, including the expert committee on DNA recombinant molecules, as well as by numerous members of the public at an open hearing just several weeks ago, and from this, the Director of NIH will determine what form the guidelines should take.

Maybe I am speaking for you, Dr. Fredrickson but I believe he plans and hopes to have a new revised set of guidelines by about April 1 for consideration by the NIH–DNA Recombinant Molecule Committee that is meeting at that time.

Dr. FREDRICKSON. Yes, they won't be issued before April, but we hope within a reasonable time thereafter.

Mr. NATCHER. Doctor, will the imposition of these guidelines result in the upgrading of laboratories in order to meet the safe lab requirements and thereby require additional funding from NIH?

Dr. KIRSCHSTEIN. We have considered this very carefully, Mr. Natcher, and on the whole, we think that, in general, upgrading will not be necessary. There may be, in same cases, a need for the development, and purchase of containment facilities, and that may cost a certain amount of money.

In general, our grantees who work in this area are very careful and do have some sort of containment facilities already. And it has seemed to us that there may not be a need for a great deal of money spent for these activities but we aren't absolutely sure, and it is possible that this may happen.

GENETIC COUNSELING

Mr. NATCHER. Doctor, what was the outcome of your workshop on methodology to evaluate the effectiveness of genetic counseling services?

Dr. KIRSCHSTEIN. That meeting was held a little bit over a year ago, sir, and the proceedings will be published in two journals in about 2 weeks.

One of them is called genetic counseling, and the other one probably will be published a little bit later is "Public Health Reports."

From that meeting came a consensus among social scientists and biological scientists that there needs to be continued efforts to assure that genetic counseling be done as carefully as possible and that studies be continued to determine how effective genetic counseling is.

Mr. NATCHER. Doctor, would you say that genetic counseling services are effective? Or do we need more research?

Dr. KIRSCHSTEIN. I think we need more research in this area. I think it is a little bit too soon to be sure that genetic counseling services are completely effective, and I think there has not been general use of genetic counseling services throughout the country as yet.

But I think it may be too soon to be absolutely sure that the general use of these services is effective, and I think we need more studies.

Mr. NATCHER. As you will recall, doctor, last year we talked about a genetic test which will indicate a predisposition toward coronary heart disease. Do you have anything new to report to the committee on this test?

Dr. KIRSCHSTEIN. There really is not a great deal of new information to report. The investigator has continued his work. The work is clearly becoming more and more focused. He originally started it in a very broad way and it is becoming more and more focused on coronary artery disease and we anticipate that that work will probably be picked up by the National Heart and Lung Institute upon renewal of that grant.

DRUG THERAPY

Mr. NATCHER. We have talked last year about the need for a rational drug therapy in order to deliver the correct dosage of drugs to avoid harmful side effects.

Specifically we talked about Valium being eliminated more slowly from the bodies of elderly patients, thus resulting in higher concentrations of that drug in the body. What has happened since last year? Have you noticed a change in the prescribing habits of physicians?

Dr. KIRSCHSTEIN. I am not sure I have. As you know, and as we told you last year, Mr. Natcher, this was one of the findings that came out of one of the studies supported in our pharmacology program.

We, as we have done always when such things occur, turned this information over to the Food and Drug Administration and I believe that they have been considering changing labeling for this drug.

I am not sure, however, from what I have heard, and I have not absolutely checked, that the prescribing habits have changed very much.

Mr. NATCHER. Doctor, would you agree with me that some of the events that have taken place in the nursing homes recently show that a great many of the elderly people have been oversedated?

Dr. KIRSCHSTEIN. I would agree with you, sir.

Mr. NATCHER. Yes; well, bless your heart. I agree with you too, doctor.

Are you supporting other research under your pharmacology program, that is currently investigating the effects of drugs other than Valium on the elderly and young children, doctor?

Dr. KIRSCHSTEIN. We have supported some research on the effect of drugs in the elderly. This came up in the course of an investigation on the adverse effects of drugs in general.

We are interested in and very anxious to support work in pediatric pharmacology. We think, however, it may be more appropriate that the National Institute on Aging support work in the area of the study of drugs in the elderly.

PEDIATRIC PHARMACOLOGY

However, in the area of pediatric pharmacology, the study of drugs in children, we are very anxious to support efforts in this direction, and if we had funds available we would undertake a program in this area.

For too long, sir, people have considered that children are little adults, and simply taken the dosage of a drug that is considered appropriate for an adult of a certain weight, and divided it appropriately to give the so-called appropriate dose to a child, based on the weight and size of the child.

We know very well now that the metabolic disposition of drugs in infants and children is different than it is in adults and that one cannot just assume that children are small adults. Studies are needed to determine what, indeed, are appropriate drugs to use in children and what indeed are appropriate dosage levels and we would like to undertake work in that regard.

Mr. NATCHER. If you would submit for the record at this point a list of drugs that are being studied along this line——

Dr. KIRSCHSTEIN. I will, sir.

[The information follows:]

DRUG STUDIES

The following drugs are currently receiving specific attention with respect to possible differences in metabolism, clearance rates, or sensitivity in aged patients when compared to younger adult patients: diazepam, quinidine, diphenylhydantoin, meperidine, and lithium carbonate. These studies are in progress at the pharmacology-toxicology research centers at Vanderbilt University and the University of California, San Francisco.

The pharmacology-toxicology program is also supporting extensive research efforts, not only in areas of pharmacology related to treatment of diseases which especially affect aged populations, but also on the effects of these disease states on the action of other drugs received by such patients. These studies include new methods of treatment of rheumatoid arthritis, development of better antihypertensive agents and of new antiarrhythmic drugs, mechanism of action of anticoagulants, and pharmacologic treatment of myocardial infarction patients.

The Boston collaborative drug surveillance program, supported by contract under an interagency agreement between the pharmacology-toxicology program and the Food and Drug Administration, is monitoring the epidemiology of adverse drug reactions. These investigators currently have available a data bank containing information on over 26,000 patients with acute drug exposure and over 40,000 patients with chronic drug exposure. One of the factors receiving special attention is the relationship of patient age to adverse experiences with therapeutic

drugs. Information received from this type of retrospective study often gives an indication of hitherto unsuspected problems which deserve special research attention.

Drugs which are being extensively studied in children in projects supported by the National Institute of General Medical Sciences include aspirin and acetominophen, diuretics, theophylline, primidone, d-amphetamine, and methylphenidate. The studies are taking place primarily at Emory University, Cornell Medical College, the University of Kansas, the University of California at San Francisco, and the State University of New York at Buffalo. Other projects which include some studies in children are concerned with the use of clonidine—to control hypertension in renal disease—naproxen—to control postoperative pain—diphenylhydantoin, isoniazid, triamterene, pseudoephedrine, and phenobarbital.

Perinatal and neonatal pharmacology are receiving attention at the pharmacology-toxicology center at Baylor University. Items of special concern are the transplacental transfer to the infant of drugs administered to the mother during labor and the transfer of drugs through the mother's milk to the nursing infant.

The NIGMS is also supporting the development of advances in methodology which have the potential for making possible the analysis of very small amounts of drugs or their metabolites. This allows studies to be made on samples of plasma, urine, or saliva from infants and small children with minimal discomfort and risk to the patient.

Any drug which is to be given to children should be systematically studied in children. The effective dose of a drug in the child may not always be extrapolated from the adult dose by reducing the adult dose in proportion to the weight of the child. The sensitivity of the less developed organ systems of the child may not be equivalent to that of an adult; the metabolic pathways in the child may not be as developed as those in the adult and, in some cases, may even be quite different. Potential for toxic effects may be greater due to the greater vulnerability of the rapidly growing and developing organism.

There are a number of drugs being given to children over relatively long periods of time for which better methods of monitoring drug levels in the child are needed. These include the anticonvulsants, especially diphenylhydantoin and phenobarbital. The psychoactive drugs, amphetamine, methylphenidate, and imipramine, for example, are often administered to children with behavioral problems, "minimal brain dysfunction," and enuresis.

Some types of new drugs being marketed are labeled as not approved for use in children, not because they are inappropriate for these patients but because the proper studies which would indicate the appropriate dose have not been done. Thus, children who need these drugs are either not receiving them or are receiving inappropriate doses. Classes of such drugs include antihypertensives, especially the diuretics. Another group of drugs used extensively in pediatric patients, sometimes for the wrong indications, is the antibiotics. There is insufficient information about the metabolism of these drugs and their distribution in the body.

Studies of the distribution, half-lives, and metabolic pathways of drugs in children would also provide information which would be essential to the proper treatment of accidental drug overdoses in children.

Mr. NATCHER. How do you work with the Food and Drug Administration? Do you notify them of your findings on specific drugs? Just what is the procedure, Doctor?

Dr. KIRSCHSTEIN. There are a number of ways in which we keep in communication with the Food and Drug Administration. When we have information about specific drugs, we do notify them on this.

In addition, members of our staff, along with members of the staff of the Food and Drug Administration, serve on an HEW committee to coordinate toxicology and other findings and exchange information in that regard.

I, myself, formerly worked for the Food and Drug Administration and have very close contacts there, and am in considerable communication with them at all times, so that we have a cooperative effort.

In addition, a research contract that we sponsor and have sponsored for a number of years with the Boston Collaborative Drug Surveillance Group is cosponsored by the Food and Drug Administra-

tion, so that we can complement each other's activities in attempting to determine what is going on in regard to drugs in this country.

Mr. NATCHER. You also said in your budget justification that about 50 individuals are actively engaged in investigation of drug reactions in humans. Is the Bureau of Drugs at the Food and Drug Administration also engaged in this type of work?

Dr. KIRSCHSTEIN. No, sir. We were talking in that statement about scientists that we would call clinical pharmacologists who are actually doing studies of the activity of drugs in man, mostly in individual patients.

The scientists or physicians at the Food and Drug Administration, in the Bureau of Drugs, are involved in the evaluation of drugs which are either on the market or for which there are applications for approval to be placed on the market. What we were indicating by that comment is that there is a great shortage in this country of clinical pharmacologists, physicians, who are in a position to do studies on drugs in humans.

Mr. NATCHER. Can you tell us, Doctor, how many new drugs are introduced into the market each year?

Dr. KIRSCHSTEIN. It is a very small number, Mr. Natcher. I do not have the figures exactly, but actually new chemical entities, I think, it is in the order of one a year, if we are quite lucky.

Now, there are a number of chemical entities which are slightly modified so that more than one variant of a drug could be placed on the market in the course of a year, but an actual new chemical entity takes a great deal of time to develop, and the processes are very slow ones.

Mr. NATCHER. Would you say, Doctor, that 50 individuals is sufficient number to be studying the mechanisms of drug action in humans.

Dr. KIRSCHSTEIN. This is a far smaller number than is needed.

BIOMEDICAL ENGINEERING RESEARCH CENTERS

Mr. NATCHER. Doctor, why are you reducing the biomedical engineering program? I believe you have an overall increase of $6 million for your Institute, but you are proposing to reduce this program. Why, Doctor?

Dr. KIRSCHSTEIN. Yes, Mr. Natcher. There are several factors that enter into this.

We had hoped, and still do hope in the next several years to develop several more biomedical engineering research centers than we now have. We now have three.

However, we feel very keenly that we should not establish any such centers until the work is of a high enough quality to merit support. We have had a number of grant applications which have not been of a quality that we have felt we should support. We are still working on this, and therefore the amount of money that we would plan to spend in this area is a little bit less than we had anticipated.

In addition, we have been very anxious to develop and set up several new burn research centers, and in order to provide funds for these within this total $6 million increase that we hope to receive, we have had to make some adjustments in the budget.

BURN PATIENTS

Mr. NATCHER. Doctor, in your opening statement to the committee you described a technique developed by a team at the University of Washington to prevent weight loss in burn patients. Is this technique available to other physicians across the country?

Dr. KIRSCHSTEIN. Yes, Dr. Curreri and his team who work at the University of Washington Burn Research Center which we support, have widely spread the information concerning this.

However, this center is in conjunction with, and right next door to the other hospital facilities there, and the technique is now available in other parts of that State and other States.

TRAUMA AND BURN RESEARCH CENTERS

Mr. NATCHER. Last year you told us that you have a goal of 15 trauma and burn research centers. Your budget shows that you will have a total of 11 such centers in 1977. Are you in a hurry to establish your goal, and to reach your goal, Doctor?

Dr. KIRSCHSTEIN. We are trying to reach our goal and we have several grant applications pending for other burn and trauma centers.

However, again, as I said concerning the biomedical engineering centers, we want very much, and will insist, that these be of the highest quality before we do put funds into them, and we are waiting to see how the grant applications will fare under review.

Mr. NATCHER. What about time, Doctor, any estimation about time?

Dr. KIRSCHSTEIN. We would hope to set up at least two more trauma and burn research centers before the end of this fiscal year, if possible, if they are of high quality.

Mr. NATCHER. Not necessarily a shortage of funds then, is that right?

Dr. KIRSCHSTEIN. Not in this area, sir.

TRAINING

Mr. NATCHER. Doctor, your budget includes the same level of funding for training in 1977 as it did in 1976. However, the distribution of the funds is different. That is to say, you are supporting more fellowships and less institutional training grants. Why is this, Doctor?

Dr. KIRSCHSTEIN. Mr. Natcher, the funding that is listed for training grants refers to the so-called old training grants that were under the old Public Health Service Act.

Under the new legislation, the National Research Service Award Act, which is pending renewal at the present time, there is support for individual fellowships and institutional fellowships.

Dr. FREDRICKSON. I wonder if I might amplify that answer a little bit further?

Mr. NATCHER. Go right ahead.

Dr. FREDRICKSON. It is true that the National Research Service Award Act of 1974—and the proposals now reported out by the House and the Senate for renewal of that authority—indicate up to 25 percent of the funds appropriated for the purpose of training under that act should go to individuals, but that institutional awards may still continue.

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However, I would call your attention to the fact that on page 335 of the appendix to the President's budget, there is a statement that fellowships are awarded to individuals under the provisions of the National Research Service Award Act for increasing the research manpower of the Nation. He further states that the emphasis will be on fellowship awards to individuals, and that it is proposed to phase out institutional awards.

This is the administration position with regard to institutional awards, to clarify Dr. Kirschstein's answer to your question.

Mr. NATCHER. Thank you.

Will you be emphasizing predoctoral or postdoctoral training support?

Dr. KIRSCHSTEIN. The emphasis of NIH as a whole, Mr. Natcher, is on postdoctoral support. In the past, the majority of the support for predoctoral training that NIH has undertaken, has been in the National Institute of General Medical Sciences, and we would hope, if it were possible, to continue to have some predoctoral activity.

Mr. NATCHER. What would be the impact of not having it, doctor?

Dr. KIRSCHSTEIN. It would clearly impact at some point in the future. At that time there would be fewer doctoral level scientists for our research pool of investigators.

This may or may not be the right number. The National Academy of Sciences currently is undertaking a study, at the request of the Congress and the Secretary of HEW, to determine what should be the appropriate numbers of trainees and the appropriate types of specialities in which training activity should take place.

Mr. NATCHER. Doctor, what is the status of your minority access to research careers program?

Dr. KIRSCHSTEIN. This is a program that the NIGMS, based on a request of Congress, undertook several years ago. We currently have obligations of $263,000 in this program.

Unfortunately, when the old training act expired, this activity was left in a difficult position and we have been unable to fund all of the types of training activities that we would like to undertake. We can, at the present time, based on the National Research Service Award Act, fund faculty fellowships in this area.

There is pending legislation, S. 988, which authorizes specific activity for this minority access to research careers program, or as we call it MARC program, to engage in other training activities for minorities, including training for research careers of undergraduates.

Mr. NATCHER. If you would, please, provide a list of the grants and the number of people being trained for the record at this point.

Dr. KIRSCHSTEIN. I will, sir.

[The information follows:]

MARC TRAINING PROGRAM

The National Institute of General Medical Sciences' minority access to research careers program—MARC—is a training program, the goal of which is to increase opportunities for advanced research training and preparation for research careers in the biomedical fields of science. A concurrent objective is to strengthen capabilities for teaching and research in those disciplines at minority institutions. These two objectives are to be achieved through the awarding of predoctoral and postdoctoral fellowships to members of the faculty at minority institutions.

The MARC program—minority access to research careers—was initiated and developed under the authority of section 301 of the Public Health Service Act. Through this program the National Institute of General Medical Sciences pro-

vided support of research training in the basic biomedical sciences for faculty members and students of minority group institutions. The enactment of the National Research Service Award Act of July—Public Law 93-348—gave us authority to fund the faculty fellowships portion of the MARC program. At the present time, the MARC program has awarded 35 individual fellowships of which 16 were awarded under section 301 and 19 under Public Law 93-348. In addition, seven research training grants were awarded to minority institutions for 5 years of support under the authority of section 301.

The following individuals, with a list of their home institutions, are being supported:

SECTION 301

Fellow and home institution	*Sponsor and institution*
Rodriguez, William Children's Hospital Washington, D.C.	Saz, Arthur Georgetown University Washington, D.C.
Brown, Grace Miles College Birmingham, Ala.	Yeilding, L. K. University of Alabama Birmingham, Ala.
Salters, Grace H. South Carolina State College Orangeburg, S.C.	Frederick, Lafayette Atlanta University Atlanta, Ga.
Bose, Sikta Howard University Washington, D.C.	Anfindsen, Christian NIAMDD, NIH Bethesda, Md.
Alexander, Carolyn Fisk University Nashville, Tenn.	Moore, Eddie Meharry Medical College Nashville, Tenn.
Debro, LaJoyce Rust College Holly Spring, Miss.	Ward, H. B. University of Mississippi University, Miss.
Martinez, Andrew University of Texas El Paso, Tex.	Packer, Lester University of California Berkeley, Calif.
Jackson, Ruby J Southern University New Orleans, La.	Derouen, T. A. Tulane University New Orleans, La.
Jones, Charles R. North Carolina Central Durham, N.C.	Johnson, Charles S. University of North Carolina Chapel Hill, N.C.
Sears, Soloman E. Clark College Atlanta, Ga.	Myers, Joseph B. Atlanta University Atlanta, Ga.
Neal, Randall Shaw University Raleigh, N.C.	Frederick, Lafayette Atlanta University Atlanta, Ga.
Payton, Cecil W. Morgan State College Baltimore, Md.	Shay, Donald E. University of Maryland Baltimoree, Md.
Pollard, Nathanael Miles College Birmingham, Ala.	Siler, William University of Alabama Birmingham, Ala.
Boyd, Lillie North Carolina Central Durham, N.C.	McManus, T. J. Duke University Durham, N.C.
Butler, William Meharry Medical College Nashville, Tenn.	Bradley, William University of Michigan Ann Arbor, Mich.
Dunston, Georgia Howard University Washington, D.C.	Herberman, Ronald NCI, NIH Bethesda, Md.

Fellow and home institution	*Sponsor and institution*
Wright, James E. Virginia Union Richmond, Va.	Faulkner, Lloyd C. Colorado State Fort Collins, Colo.
Banks, Richard A. Hampton Institute Hampton, Va.	Haughton, Geoffrey University of North Carolina Chapel Hill, N.C.
Washington, Betty J. Albany State College Albany, Ga.	Frederick, Lafayette Atlanta University Atlanta, Ga.
Ray, Gautam Southern University Baton Rouge, La.	Liu, Y. King Tulane University New Orleans, La.
Wells, Alexander Tennessee State College Nashville, Tenn.	Proctor, Charles D. Meharry Medical College Nashville, Tenn.
Jones, Johnnye M. Morgan State College Baltimore, Md.	Frederick, Lafayette Atlanta University Atlanta, Ga.
Fennell, Pearlie M. Texas Southern Houston, Tex.	Matthews, Kathleen S. Rice University Houston, Tex.
Latimer, Steve Langston University Langston, Okla.	Carpenter, Mary P. Oklahoma Medical Research Foundation Oklahoma City, Okla.
Barranda, Erlinda Norfolk State College Norfolk, Va.	Brush, Robert Syracuse University Syracuse, N.Y.
Davis, Elaine Morgan State College Baltimore, Md.	Jackson, Julius Meharry Medical College Nashville, Tenn.
Douglas, James D. Meharry Medical College Nashville, Tenn.	Bradley, Robert University of Michigan Ann Arbor, Mich.
Duncan, Howard B. North Carolina Central Durham, N.C.	Weatherly, Norman University of North Carolina Chapel Hill, N.C.
Demotta, Gladys University of Puerto Rico San Juan, P.R.	Del Castillo, Jose University of Puerto Rico Medical Science Campus San Juan, P.R.
Michael, George Federal City College Washington, D.C.	Bailey, J. M. George Washington University Washington, D.C.
Nicholson, Jesse Howard University Washington, D.C.	Lutzner, Marvin NCI, NIH Bethesda, Md.
Ray, Rasharaman Howard University Washington, D.C.	Catterall, William NHLI, NIH Bethesda, Md.
Salters, Walter South Carolina State Orangeburg, S.C.	Myers, Joseph B. Atlanta University Atlanta, Ga.
Titus-Dillon, Pauline Howard University Washington, D.C.	Neufeld, Elizabeth NIAMDD, NIH Bethesda, Md.
Whiten, Joycelyn T. King/Drew Medical Center Los Angeles, Calif.	Junge, Douglas University of California Los Angeles, Calif.

Mr. NATCHER. Doctor, you have made an excellent presentation of your budget request for the fiscal year 1977.

Dr. KIRSCHSTEIN. Thank you, Mr. Natcher.

Mr. NATCHER. Mr. Shriver?

Mr. SHRIVER. Thank you, Mr. Chairman. I know that your Institute is doing quite a lot of research in connection with burn injuries. What statistics do we have concerning the number of people yearly affected by burns?

Dr. KIRSCHSTEIN. Yes, sir. The number of people who are severely burned each year, severely enough to require intensive care, is 70,000. Almost 10,000 of these die a year. Twenty-nine percent of these are children under the age of 15 and the deaths in males outnumber those in females very considerably.

Mr. SHRIVER. Are the number of your new grants dropping?

Dr. KIRSCHSTEIN. Yes, sir. For fiscal 1977 there will be a decrease of about 269 new grants that we can award.

Mr. SHRIVER. Why the decrease?

Dr. KIRSCHSTEIN. The number of grants that were awarded in 1976 was considerable and this, therefore, increases the number of noncompeting grants that we will have in 1977, and for the total moneys, therefore, we can support fewer new grants.

Mr. SHRIVER. You mentioned, in answer to a question of Mr. Natcher, three biomedical engineering centers. Where would they be?

Dr. KIRSCHSTEIN. One is at the Massachusetts Institute of Technology. One is at the University of Washington in Seattle, and the third one is at Stanford University in Palo Alto, Calif.

We hope to have several others and have grant applications pending at the present time.

Mr. SHRIVER. What is involved relative to the amount of money when a new one is established? Does it vary?

Dr. KIRSCHSTEIN. It varies. These research center grants have expenditures usually in the first year in the order of $250,000 to $300,000, and as they begin to build up competence, there usually are increased expenditures over the next several years.

Mr. SHRIVER. You covered the subject very well for the chairman, and I have no further questions.

Mr. NATCHER. Mr. Early?

Mr. EARLY. Thank you, Mr. Chairman.

Doctor, is one of the fundamental purposes of your Institute the investigation of genetics?

Dr. KIRSCHSTEIN. Yes, sir.

DIABETES

Mr. EARLY. What is the relationship of genetics and environment to diabetes?

Dr. KIRSCHSTEIN. Diabetes is a disease that is probably caused by a number of complex factors, of which one important factor is genetics. The environment undoubtedly plays an important role in this also.

PEDIATRIC PHARMACOLOGY

Mr. EARLY. Doctor, in answer to Mr. Natcher's question you stated you could use more money for an expanded pharmacology study on the

effects of drugs on children. Could you tell us how much money you could use for that purpose?

Dr. KIRSCHSTEIN. We would anticipate as a beginning activity in pediatric pharmacology, we could fund a number of grants for about $1 million.

Mr. EARLY. What did you request of OMB on that?

Dr. KIRSCHSTEIN. The request for the pharmacology program as a whole for this year was about $25 million.

PHARMACOLOGY MANPOWER

Mr. EARLY. On page 20 you say you need more clinical pharmacologists, how many more do you need?

Dr. KIRSCHSTEIN. It is very difficult to determine. We said that 50 was a very small number. I would think that certainly bringing that number up to 70 or 75 or close to 100 would be reasonable. In addition, the National Academy of Sciences currently has this under study and hopefully will be giving us some figures.

Mr. EARLY. How many could we train in the program?

Dr. KIRSCHSTEIN. The number is very difficult to determine, because one of the things that we feel very keenly about is that the training should be of a very high quality and we would prefer to train lesser numbers of individuals who are of very high quality than very large numbers who are not highly qualified.

NEW RESEARCH GRANT AWARDS

Mr. EARLY. Now, to Mr. Shriver you said the grants in 1977 are 269 less than in 1976.

Dr. KIRSCHSTEIN. New awards.

Mr. EARLY. New awards, and I think you also said that was because of lack of money.

Dr. KIRSCHSTEIN. That was correct, sir.

Mr. EARLY. It was money only to continue funding existing grant awards.

Dr. KIRCHSTEIN. That was because the number of noncompeting awards currently on the books and continued for next year has increased and, therefore, with the totality of the money we can only do less, make fewer new awards.

Mr. EARLY. Tell me, Doctor, how many of the grant awards terminate at the end of their first granting period, and how many call for an extension of their grants to complete their studies?

Dr. KIRCHSTEIN. This is a very difficult answer to give. We would estimate that considerably more than half of those grants that reach the end of their first granting period ask for a renewal of activities. They must compete again, and of those, fewer of them are awarded, not all of them are awarded again.

Mr. EARLY. 50 percent.

Dr. KIRSCHSTEIN. Probably more than 50 percent apply for renewal but they must, just as new applicants compete for the moneys.

Mr. EARLY. I ran across a problem in the State justice subcommittee with LEAA. That program was spending close to $1 billion compiling some five studies that no one is reading. They are just sitting

in a corner accumulating dust. Can you assure this subcommittee that that is not the case with these grant awards, 50 percent of which, you have stated, are renewed?

Dr. KIRSCHSTEIN. A grant is usually given for 3 to 5 years. More grants are given now for 3 years than for 5, and at the end of that 3-year period, the scientist has made a certain amount of progress. He almost always has further ideas to expand this effort, and so he will submit a renewal request to continue the activity. This is a continued generation of new information. In addition, as scientists develop new knowledge, they publish this information in technical journals so as to inform their colleagues.

Mr. EARLY. Thank you, Doctor.

Thank you very much, Mr. Chairman.

Mr. NATCHER. Mr. Michel?

RESEARCH

Mr. MICHEL. Most of your programs cut across Institute lines, with corollary research conducted by a number of other Institutes. Do you coordinate your activities with theirs?

Dr. KIRSCHSTEIN. The National Institute of General Medical Sciences, particularly because our programs are basic to other Institutes, we are especially concerned with the need for coordination of our activities with those of other Institutes.

Mr. MICHEL. What kind of a mechanism do you have to coordinate research activities with these other Institutes and to insure timely transfer of research findings?

Dr. KIRSCHSTEIN. In addition to the extensive and prevalent exchange of information in the scientific literature, the Institute scientific staff engages in informal discussions concerning its activities with staff of other Institutes. On occasion, when several Institutes have specifically overlapping interests and activities, the senior staffs of each meet together along with staff of the Office of the Director, NIH, and develop a memorandum of understanding which outlines the means of coordination, and the responsibilities of each Institute. When a basic research endeavor supported by NIGMS becomes focused in an area of concern to one of the categorical Institutes, such research activities are transferred to that Institute for support at the appropriate renewal time. Research findings developed by NIGMS grantees for which a timely transfer of information is in order, such as the report of an adverse drug reaction, are immediately communicated to the appropriate agencies as, for example, the Food and Drug Administration.

Mr. MICHEL. Do you work with these other Institutes prior to launching into research in a particular area in order to insure complementary rather than parallel efforts?

Dr. KIRSCHSTEIN. NIGMS will often sponsor workshops and discussions with other Institutes prior to launching into new research endeavors in particular areas so as to develop complementary activities which encompass the entire scientific field.

Mr. MICHEL. Do you ever get into disputes with other Institutes as to who does what research?

Dr. KIRSCHSTEIN. We have not had any disputes with other Institutes as to who does what research.

Mr. MICHEL. Dou you ever have joint review panels with any of the other Institutes if there is mutual interest in a certain line of research?

Dr. KIRSCHSTEIN. The vast majority of grant applications assigned to NIGMS are reviewed by the Initial Review Groups of the Division of Research Grants which has the responsibility for the review of the majority of grant applications received at NIH. On occasion, a grant application may be given a dual Institute assignment indicating that there are two Institutes with interest in the particular area. In such a case, the staffs of the two Institutes discuss the issue and reach a conclusion concerning the appropriate funding if such an application is approved.

DIABETES

Mr. MICHEL. What about diabetes, for instance? How much money are you devoting to diabetes research, and how specifically do you coordinate with other Institutes in this regard?

Dr. KIRSCHSTEIN. The NIGMS is currently spending $730,000 on research efforts directly related to diabetes. These efforts are in areas relevant to the five NIGMS research program activities and are broadly based. If and when such research activities become more specifically focused on certain aspects of diabetes such as heart disease, pancreatic transplants, or therapeutic tests of new antidiabetic drugs, the NIGMS would transfer such activities to the appropriate categorical Institutes. Furthermore, as required under the Diabetes Act, the NIGMS is a member of the DHEW Diabetes Mellitus Coordinating Committee through which diabetes related activities of all units of the Department are coordinated.

BURN VICTIMS

Mr. MICHEL. This new intravenous feeding formula that has apparently been developed for burn victims, how far along is it and when could it be placed into widespread use?

Dr. KIRSCHSTEIN. The combined use of an intravenous feeding formula and feeding by nasogastric tube which was developed by Dr. Willian Curreri at the University of Washington is available for widespread use and indeed is now being used by others throughout the country in the treatment of burn victims.

Mr. MICHEL. Based on your findings to date, what is its potential for saving lives?

Dr. KIRSCHSTEIN. Prior to the use of such feeding techniques, 100 percent of persons with 85 percent total body surface burns died as a result of acute loss of greater than 30 percent of body weight. With the use of this feeding technique and other measures, 50 percent of young adults with such severe burns now survive.

Mr. MICHEL. There is also an artificial skin which has been developed. Where do we stand with this research, and when can we expect human applicability?

Dr. KIRSCHSTEIN. The development of this artificial skin is in a very preliminary stage and was only reported at the end of 1975. Such an artificial skin is currently undergoing intensive tests in animals. The results appear very encouraging but it will be some years before it will be possible to use such material in humans.

BIOMATERIALS

Mr. MICHEL. These new steel and ceramic joints that are being developed, do they have considerable potential for aiding arthritis victims, and if so, about how far down the road are we talking about?

Dr. KIRSCHSTEIN. Steel and ceramic joints have been used for some time. However, they undergo wear and tear with use and replacement is required. A new biomaterial, bioglass, has been developed which binds to bone and does not appear to undergo wear and tear; these artificial joints coated with bioglass are currently being tested in animals. If such tests are satisfactory, it is anticipated that these new artificial joints may be available for use in man in several years. The potential of these replacement joints for aiding arthritis victims will have to be evaluated carefully.

BASIC RESEARCH

Mr. MICHEL. You refer in your statement to numerous research efforts that are in progress. Can you point to areas where research has recently been completed and has produced beneficial results which are currently in active use?

Dr. KIRSCHSTEIN. The human organ is made up of innumerable interrelated structures and processes of enormous complexities. Because of his interrelatedness, our understanding of a particular process is limited and dependent on our understanding of the other parts and how they fit together. In this sense, the basic research supported by this Institute has a long way to go before it is completed; new findings in the laboratory may require that interpretations and conclusions based on earlier findings be modified. However, as basic research continues, findings and results are continuously applied to practical and clinical problems. As examples of the latter, we can point to the work of Dr. J. Goldstein of the basic defect in familial hypercholesterolemia, a common genetic disorder associated with heart disease, the diagnosis and treatment of which have been facilitated as a result of his work. The laboratory of the clinical pharmacologist, Dr. P. Calabresi, has brought the drug, azarbine, to a stage of general usefulness in the treatment of severe psoriasis. Another important advance was the recently developed technique for visualizing chromosome defects. This technique, worked out by Dr. Latt has many applications and is used as a tool in basic research as well as in the detection of disease of carcinogenic compounds.

BURN RESEARCH

Mr. MICHEL. What have you done regarding the Senate report language calling on you to work with the Health Services Administrator in developing a comprehensive burn program? I note you were to have had a report completed in January. Has it been, and if so, what will you be doing?

Dr. KIRSCHSTEIN. The National Institute of General Medical Sciences has submitted a preliminary report concerning its activities in regard to support of burn research. A copy of this report will be submitted for the record. As indicated in this report, a member of the

NIGMS staff is serving on an interagency burn center task force which is developing a comprehensive burn program. This task force is headed by a representative of the Health Services Administration. The outline of the proposed task force report which will be submitted in April is given in the report submitted to the Senate Appropriations Subcommittee in February 1976.

[CLERK'S NOTE.—This report appears at the end of this volume with other special reports prepared by the National Institutes of Health for the committee.]

Mr. NATCHER. Mr. Roybal.

PROGRAM REQUIREMENTS

Mr. ROYBAL. Last year you received $187 million. This year you requested $193.4 million. This will not even cover inflation. Will you have to cut back your research programs? If so which ones? Will you have to lay any people off? If so, how many? If no to all questions, how will you keep the program operating at last year's level?

Dr. KIRSCHSTEIN. Although there is a small increase in dollars for research grants in each of our programs except biomedical engineering the net effect will be that the NIGMS will be able to award fewer new and competing renewal grants under the budget request of $193.4 million for fiscal year 1977. We will be able to fund approximately 485 fewer competing grants of which about 269 would be new awards and about 216 would be competing renewal grant applications. These cutbacks will affect all our five programs; namely, cellular and molecular basis of disease, genetics, pharmacology-toxicology, clinical and physiological sciences, and biomedical engineering. The largest cutbacks will be in the programs which support the basic scientific disciplines, cellular and molecular basis of disease and genetics.

The number of personnel allotted to NIGMS for fiscal year 1976 is 164. In fiscal year 1977, the budget request specifies an allotment of 153 persons. Thus, when we fill the current vacancies to reach 164 we will, if the fiscal year 1977 personnel allotment holds, have to reduce the staff by 11.

GENETICS

Mr. ROYBAL. Does your genetics program raise any moral or religious questions? Have you issued any guidelines in this area? What do they say?

Dr. KIRSCHSTEIN. Grantees of the NIGMS genetics program, as those of all NIH programs, are required to follow the published NIH guidelines in regard to protection of human subjects.

Furthermore, as a result of an initiative by a number of scientists, including several supported by NIGMS, a moratorium on genetics research involving studies of recombinant DNA molecules was proposed and undertaken. As a result of a series of meetings, the first one of which was a year ago, a set of preliminary guidelines related to such research has been developed. Based on extensive review of these guidelines both by an expert committee and representatives of the public, NIH hopes soon to issue definitive guidelines to be followed in doing research related to recombinant DNA molecules. These guidelines will address the safety and moral issues involved. When issued we will furnish copies to the committee.

BURN RESEARCH

Mr. ROYBAL. Have you disseminated the results of your work involving weight loss and burns? How many hospitals now use the formula you developed to insure adequate caloric intake?

Dr. KIRSCHSTEIN. The results of the work supported by NIGMS related to prevention of weight loss in persons suffering severe burns have been widely disseminated through publication in nationally circulated medical journals and through presentation at national medical and scientific meetings. The formula used to insure adequate caloric intake in severly burned persons is available to be used at burn centers and major hospitals throughout the country.

PHARMACOLOGY-TOXICOLOGY

Mr. ROYBAL. You have been working in the area of pharmacology and diabetics. Have you worked closely with the Institute of Arthritis, Metabolic and Digestive Diseases? If so, detail the results of your combined effort.

Dr. KIRSCHSTEIN. The NIGMS has supported work in the area of pharmacology as related to diabetes. In this area 10 grants are supported, being particularly related to studies of insulin and oral diabetic agents and to glucagon and somatostatin which are relatively newly studied chemicals which regulate blood sugar. These studies are coordinated with those of the National Institute of Arthritis, Metabolic and Digestive Diseases and other agencies through the Interagency Diabetes Mellitus Coordinating Committee and have resulted in the development of a plan outlining the requirements for further specific research efforts.

PROGRAM AREAS

Mr. CONTE. Dr. Kirschstein, would you outline the areas in which you have research programs which interact with the programs of some of the other institutes.

Dr. KIRSCHSTEIN. All five programs of the National Institute of General Medical Sciences have areas of interaction with the programs of other institutes.

Studies supported by the cellular and molecular basis of disease program which involve the development of knowledge concerning cell structure, the cellular organelles and cell membranes interact with programs of the National Cancer Institute in which knowledge is sought concerning the ways in which malignant cells differ from normal cells.

Studies concerning fundamental knowledge of the genetic constitution of bacteria and lower organisms, other mammals and man, and of human genetic defects interrelate with the sickle cell disease and hypertension and myocardial infarction programs of the National Heart and Lung Institute; the diabetes and inborn error of metabolism programs of the National Institute of Arthritis, Metabolism and Digestive Diseases; the child development program of the National Institute of Child Health and Human Development; the programs of the National Cancer Institute in regard to the role of inheritance in the development of cancer and the possible viral etiology of cancer; the programs of the National Eye Institute which study inherited ophthal-

mological conditions; the mechanisms of chromosome damage caused by many environmental pollutants of concern to the National Institute of Environmental Health Sciences and the elucidation of new genetic forms resulting from procedures leading to recombinant nucleic acid molecules of concern also to the National Institute of Allergy and Infectious Diseases.

Studies of the mechanisms of action of drugs and the adverse effects which they may cause interact with the program of NCI in regard to cancer chemotherapeutic agents; the programs of the NIAMDD related to antidiabetic drugs and the therapy of certain diseases such as psoriasis; the studies of the use of new drugs in the control of epilepsy undertaken by the National Institute of Neurological and Communicative Disorders and Stroke; the preventive effects of drugs in hypertension and myocardial infarction as studied by NHLI: the general toxicity studies of the NIEHS and the FDA; and the differences in reaction to drugs seen in aging and childhood populations which are also of concern to the National Institute on Aging and the NICHD.

The clinical and physiological sciences program supports studies of the basic mechanisms of anesthetic agents which interact with the studies of the Division of Pulmonary Diseases of NHLI. Studies of the basic cellular and physiologic changes which occur as a result of severe trauma are interrelated with programs such as the kidney program of the NIAMDD.

The studies supported by the biomedical engineering program involve the development of instrumentation, devices, and biomaterials which are of importance to the artificial organs programs of the NHLI and NIAMDD in regard to artificial heart and lungs or replacement joints. The development of new diagnostic X-ray techniques supported by this program are complementary to the diagnostic radiology program of the NCI in regard to the early detection of cancer.

COOPERATIVE EFFORTS—EMERGENCY MEDICAL SYSTEMS

Mr. CONTE. Have you continued the cooperative efforts between the trauma centers and emergency medical systems?

Dr. KIRSCHSTEIN. Cooperative efforts continue between the trauma research centers and the emergency medical systems units which have been established by the Health Services Administration. NIGMS trauma centers which engage in research are located in the same areas and collaborate with the emergency medical systems units in Boston, San Francisco, and Seattle. A comprehensive burn program is being developed by an interagency burn center task force. Such a program will coordinate efforts of the NIGMS burn research centers, the emergency medical service units, and other groups involved in treatment and rehabilitation.

COMPUTER DIAGNOSIS

Mr. CONTE. Has any progress been made in computer diagnosis?

Dr. KIRSCHSTEIN. We assume you refer to the work described in last year's testimony concerning computer-assisted transmission of X-ray pictures via telephone lines. In this particular case, technical and economic obstacles are temporarily delaying further development and widespread use of this technology but work is continuing.

Computers have become indispensable components of almost all modern, complex equipment, including diagnostic instruments. For in-

stance, they are essential tools in recently announced techniques for measuring genetic material, DNA, in human chromosomes—an important capability in the diagnosis of genetic disease. Another application of computers has been made by a scientist at Irvine, Calif., whose use of computers has allowed him to detect more lesions on chest X-rays than was previously possible.

In a wider sense, the term, computer diagnosis, is used to refer to systems whereby data from physical examination, clinical laboratory tests, and other sources are fed into a computer that is programed to assemble these data, match them against stored information, and then select the diagnosis which fits the patient data. Work of this kind is supported particularly by the National Center for Health Services Research and Development, Health Resources Administration, and the Division of Research Resources, NIH.

ACUPUNCTURE

Mr. CONTE. Last year you indicated you were doing substantial research into acupuncture, well over $100,000 worth. What has come of this research?

Dr. KIRSCHSTEIN. The NIGMS continues to support research on acupuncture. In fiscal year 1975 the Institute funded seven grants for a total of $230,000. Some of the work involves studying the sensory changes that occur as a result of stimulation of acupuncture points by needle twirling or electrostimulation. Both animal and human studies are being performed and data are being collected, but have not yet been analyzed. In a clinical study at the University of California, on the use of acupuncture for asthma, very preliminary data show slight improvement and reduction in required medication for chronic asthma following real as opposed to placebo acupuncture. An important study, now in its first year, will attempt to determine which nerve pathways in the spinal cord are involved in mediating the effect which results from stimulation of the "hoku" point, one of the most commonly used acupuncture points between the thumb and second finger. Such information could provide a physiological basis for acupuncture.

GENETIC RESEARCH

Mr. CONTE. What are the ultimate goals of your genetic research?

Dr. KIRSCHSTEIN. The ultimate goals of the genetics research which we support are: the elucidation of the role of heredity in many of the common as well as rarer diseases of man; the development of diagnostic tests to predict the possible occurrence of many inherited diseases in unborn children; and the prevention and treatment of inherited diseases, and congenital anomalies.

PROFESSIONAL JUDGMENT NEEDS

Mr. CONTE. Do you feel that, in your professional judgment, the National Institute of General Medical Sciences is funded adequately to perform the research that is needed?

Dr. KIRSCHSTEIN. In my professional judgment, in order to adequately perform the research that is needed, NIGMS will require a total increase of about $20 million. This would include an increase of

$15 million for research grants to fund about 379 new research grant applications, three new research centers and $5 million for 174 new fellowships. I recognize, of course, that Federal funds are limited and must be distributed among competing national priorities. These policy decisions, as you well know, are properly the concern of both the administration and the Congress.

STAFFING NEEDS

Mr. CONTE. Do you feel that the Institute is adequately staffed?

Dr. KIRSCHSTEIN. The number of personnel allotted to NIGMS for ficscal year 1976 is 164 and this will provide us with adequate staffing. However, in fiscal year 1977, the budget request specifies an allotment of 153 persons which would not allow adequate staffing and would require a reduction of the staff by 11, after filling the current vacancies to reach 164.

CHROMOSOME DAMAGE

Mr. CONTE. Is there conclusive evidence to show that pollution can cause chromosome damage?

Dr. KIRSCHSTEIN. Certain chemicals which are known to pollute the air and water have been shown to cause chromosome damage under certain conditions and in certain concentrations. However, since air pollution consists of a changing complex of substances which are present in verifying amounts, it is not possible to state that there is conclusive evidence to show that pollution generally can cause chromosome damage. As evidence concerning the causation of such damage by specific chemicals is developed, NIGMS will keep the National Institute of Environmental Health Sciences informed so that it may undertake further studies.

BURN RESEARCH

Mr. CONTE. An article in the Washington Star in December mentioned a development in artificial skin for burn patients. Can you tell us how this has progressed? When will it be used with human patients?

Dr. KIRSCHSTEIN. The development of an "artificial skin" is in a very preliminary stage and was only reported at the very end of 1975. The use of this material is currently being tested in animals in order to assess in detail, both its therapeutic value and any adverse effects. The results appear very encouraging but it will be some years before it will be possible to use such material in humans.

FUNDING

Mr. CONTE. Why has the number of new grants dropped to 74 from 343 in 1976?

Dr. KIRSCHSTEIN. The number of new grants to be funded in fiscal year 1976 is approximately 343. Since these will be funded for a period of 3 to 5 years, they will be among the noncompeting grants in fiscal year 1977, allowing NIGMS to fund far fewer new grants, in fact only 74, for the increase of $6 million allowed in the fiscal year 1977 budget.

Mr. NATCHER. Doctor, thank you very much. We want to thank you and your associates for appearing.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Amounts Available for Obligation

	1976 Estimate	1977 Estimate
Appropriation	$146,461,000	$193,435,000
Request pending	40,851,000	---
Subtotal, adjusted appropriation	187,312,000	193,435,000
Comparative transfer from:		
"Office of the Director" (for the Standard Level User Charge)	+76,000	---
Total, obligations	187,388,000	193,435,000

National Institute of General Medical Sciences

Budget Mechanism

	1976			1977		
	Number	FTE	Amount	Number	FTE	Amount
Research Grants:						
Regular:						
Non-competing	1,228		$70,749,000	1,548		$99,183,000
Competing	348		20,835,000	132		8,559,000
New	343		17,762,000	74		3,923,000
Supplemental	(138)		2,300,000	(101)		2,000,000
Subtotal	1,919		111,646,000	1,754		113,665,000
Special:						
Pharmacology-Toxicology Research Centers	9		4,584,000	9		5,643,000
Diagnostic Radiology Research Centers	2		1,200,000	2		1,200,000
Biomedical Engineering Research Centers	5		2,200,000	5		2,200,000
Anesthesiology Research Centers	5		3.363,000	5		3,190,000
Trauma and Burn Research Centers	9		2,078,000	11		4,400,000
Genetic Research Centers	10		5,768,000	10		6,500,000
Molecular Pathology Research Centers	1		488,000	1		425,000
Research Career Programs	216		5,376,000	216		5,376,000
Scientific Evaluation	---		516,000	---		516,000
Subtotal	257		25,573,000	259		29,450,000
Total Research Grants	2,176		137,219,000	2,013		143,115,000
Fellowships:						
Noncompeting	365		18,348,000	346		20,200,000
Competing	---		---	---		---
New	---		---	216		3,031,000
Supplemental	(27)		50,000	---		---
Subtotal	365	1,383	18,398,000	562	1,636	23,231,000
Training Grants:						
Noncompeting	288		20,953,000	154		17,620,000
Competing	---		---	---		---
New	---		---	---		---
Supplemental	(225)		1,500,000	---		---
Subtotal	288	3,104	22,453,000	154	2,456	17,620,000
Total, Grants	2,829		178,070,000	2,729		183,966,000
Research & Development Contracts	11		1,500,000	11		1,500,000
Intramural Research & Direct Operations	---		7,040,000	---		7,156,000
Program Management	---		702,000	---		713,000
Standard Level User Charge	---		76,000	---		100,000
TOTAL	2,840		187,388,000	2,740		193,435,000

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DHEW - National Institutes of Health

Crosswalk - F.Y. 1976 Column of F.Y. 1977 Justification

INSTITUTE: National Institute of General Medical Sciences

(Dollars in Thousands)

Program \ Mechanism	Research Grants				Training Programs		Research and Development Contracts	Intraumural Research & Direct Operations	Program Management	Total
	Regular Program		Specials							
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Cellular & Molecular Basis of Disease...	$22,950	$16,572	$488	$2,438	$11,271	$9,236	---	---	---	$62,955
2. Genetics.....	29,102	12,947	5,768	2,299	1,662	4,546	$409	---	---	56,733
3. Pharmacology-Toxicology.....	9,375	4,359	4,584	626	2,021	3,090	333	$462	---	24,850
4. Clinical & Physiological Sciences...	2,278	3,524	5,441	204	5,276	1,042	---	---	---	17,765
5. Biomedical Engineering.....	7,044	3,495	3,400	325	2,223	484	758	---	---	17,729
6. Intramural Research and Direct Operations.....	---	---	---	---	---	---	---	6,654	---	6,654
7. Program Management...	---	---	---	---	---	---	---	---	$702	702
Total obligations....	70,749	40,897	19,681	5,892	22,453	18,398	1,500	7,116	702	187,388

DHEW - National Institutes of Health

Crosswalk - F.Y. 1977 Column of F.Y. 1977 Justification

INSTITUTE: National Institute of General Medical Sciences

(Dollars in Thousands)

Program \ Mechanism	Research Grants				Training Programs		Research and Development Contracts	Intramural Research & Direct Operations	Program Management	Total
	Regular Program		Specials							
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Cellular & Molecular Basis of Disease...	$36,394	$5,291	$425	$2,289	$8,098	$11,846	---	---	---	$64,343
2. Genetics.....	38,188	4,082	6,500	2,305	1,662	5,353	$409	---	---	58,499
3. Pharmacology-Toxicology.....	11,415	1,450	5,643	630	1,638	3,590	333	$467	---	25,166
4. Clinical & Physiological Sciences...	5,706	1,729	7,590	325	4,229	1,678	---	---	---	21,257
5. Biomedical Engineering.....	7,480	1,930	3,400	343	1,993	764	758	---	---	16,668
6. Intramural Research and Direct Operations.....	---	---	---	---	---	---	---	6,789	---	6,789
7. Program Management...	---	---	---	---	---	---	---	---	$713	713
Total obligations....	99,183	14,482	23,558	5,892	17,620	23,231	1,500	7,256	713	193,435

Summary and Explanation of Changes

1976 Estimated obligations	$187,388,000
1977 Estimated obligations	193,435,000
Net change	+6,047,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Within-grade pay increase cost..	---	$28,000	---	+$30,000
2. FTS rate increase.....	---	40,000	---	+10,000
3. Postage increase.....	---	83,000	---	+25,000
4. Annualization cost of October 1975 pay raise.....	---	190,000	---	+48,000
5. Payment to "NIH Management Fund" for centrally furnished services.....	---	1,819,000	---	+95,000
6. Standard Level Users Charge.....	---	76,000	---	+24,000
Subtotal.....	---	---	---	+232,000
B. Program:				
1. Research grants:				
a. +720 noncompeting continuation research grants....	---	70,749,000	---	+42,620,000
b. +206 competing (new, continuation and supplemental)..	---	40,897,000	---	+14,482,000
2. +6 Special programs.....		25,573,000		+3,877,000
3. Fellowships:				
a. +216 new fellowships.....	---	---	---	+3,031,000
b. +53 noncompeting fellowships.....	---	15,423,000	---	+4,075,000
Subtotal.....	---	---	---	+68,085,000
Total, increases.....	---	---	---	+68,317,000
Decreases:				
A. Built-in:				
1. One less day of pay.....	---	3,401,000	---	-13,000
B. Program:				
1. Research grants:				
a. -400 noncompeting completed or converted to competing status.....	---	70,749,000	---	-14,186,000
b. -691 competing completed or converted to noncompeting continuations.....	---	40,897,000	---	-40,897,000
2. Fellowships:				
a. -27 supplemental fellowships.....	---	50,000	---	-50,000
b. -72 noncompeting fellowships completed or converted to competing status.....	---	2,925,000	---	-2,223,000

Summary and Explanation of Changes - Continued

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
3. Training grants:				
a. -225 supplemental training grants	---	1,500,000	---	-1,500,000
b. -134 noncompeting completed or converted to competing status	---	20,953,000	---	-3,333,000
4. Intramural research and direct operations	---	7,116,000	---	-68,000
5. Positions	164	---	-11	---
Subtotal		---		-62,257,000
Total, decrease	---	---	---	-62,270,000
Total, net change	164	---	-11	+6,047,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
15	Cellular and Molecular Basis of Disease.....	$53,956,000	$62,955,000	$64,343,000	+$1,388,000
17	Genetics.....	50,599,000	56,733,000	58,499,000	+1,766,000
19	Pharmacology-Toxicology.	22,329,000	24,850,000	25,166,000	+316,000
21	Clinical and Physiological Sciences.....	16,527,000	17,765,000	21,257,000	+3,492,000
23	Biomedical Engineering..	16,847,000	17,729,000	16,668,000	-1,061,000
25	Intramural Research & Direct Operations.....	6,578,000	6,578,000	6,689,000	+111,000
	Positions.....	129	140	129	-11
26	Program Management.....	702,000	702,000	713,000	+11,000
	Positions.....	24	24	24	-0-
	Standard Level User Charge.....	76,000	76,000	100,000	+24,000
	Total obligations.....	167,614,000	187,388,000	193,435,000	+6,047,000
	Positions.....	153	164	153	-11

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions...	164	153	-11
Full-time equivalent of all other positions.....	6	6	-0-
Average number of all employees.....	162	156	-6
Personnel compensation:			
Permanent positions.....	$2,855,000	$2,864,000	+$9,000
Positions other than permanent.....	92,000	93,000	+1,000
Other personnel compensation.....	80,000	81,000	+1,000
Subtotal, personnel compensation..	3,027,000	3,038,000	+11,000
Personnel benefits.....	374,000	383,000	+9,000
Travel and transportation of persons..	100,000	100,000	-0-
Transportation of things.....	20,000	20,000	-0-
Rent, communications, and utilities...	240,000	275,000	+35,000
Printing and reproduction.....	220,000	220,000	-0-
Other services:			
Project contracts.....	1,500,000	1,500,000	-0-
Payment to NIH Management Fund.....	1,895,000	2,014,000	+119,000
Other.....	1,792,000	1,769,000	-23,000
Supplies and materials.....	75,000	75,000	-0-
Equipment.....	75,000	75,000	-0-
Grants, subsidies, and contributions..	178,070,000	183,966,000	+5,896,000
Total obligations by object.....	187,388,000	193,435,000	+6,047,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1976 Senate Report	
1. The Committee believes that services relating to burn research and victims should in most cases be conducted by the Health Services Administration. However, the Committee feels strongly that such services should begin immediately and a close coordination of research and service is vital. NIGMS is therefore directed to work with the Health Services Administration in developing an effective and useful comprehensive burn center program (page 52).	The NIGMS is working closely with the Health Services Administration in developing a comprehensive Burn Center program and expects to have a report completed in January 1976.

Authorizing Legislation

Legislation	1977 Authorized	1977 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	$152,584,000[2/]
Title IV, Part I - National Research Service Awards Act[1/]		40,851,000[2/]

1/ Authorization expires June 30, 1975; extension legislation is pending.

2/ Funding estimate only.

National Institute of General Medical Sciences

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1967	$130,734,000	$136,172,000	$138,672,000	$138,672,000
1968	152,295,000	152,295,000	156,295,000	152,295,000
1969	157,650,000	153,123,000	158,123,000	155,386,500
1970	146,685,000	146,685,000	167,397,000	157,041,300
1971	141,398,000	159,094,000	164,094,000	159,094,000
1972	143,274,000	161,364,000	172,192,000	166,348,000
1973	173,377,000	180,588,000	203,417,000	180,588,000 1/
1974	138,573,000	175,778,000	183,500,000	168,329,000 2/
1975	168,399,000	178,178,000 3/	198,070,000	187,470,000
1976	161,706,000	146,537,000	146,537,000	
Items not considered		(40,851,000)	(40,851,000)	
1977	193,435,000			

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 as authorized by Public Law 93-192.

3/ Excludes Research & Development Contracts which were not considered by the House due to pending authorization.

Note: The figures presented in this Table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of General Research Support Grants is no longer the function of this Institute. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes.

National Institute of General Medical Sciences

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	146,461,000	146,461,000	
Items not considered		(40,851,000)	(40,851,000)	
1977	193,435,000			

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 as authorized by Public Law 93-192.

3/ Excludes Research & Development Contracts which were not considered by the House due to pending authorizing.

Justification

National Institute of General Medical Sciences

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Cellular and Molecular Basis of Disease.....	$53,956,000	$62,955,000	$64,343,000	+$1,388,000
Genetics.....	50,599,000	56,733,000	58,499,000	+1,766,000
Pharmacology-Toxicology.....	22,329,000	24,850,000	25,166,000	+316,000
Clinical and Physiological Sciences.....	16,527,000	17,765,000	21,257,000	+3,492,000
Biomedical Engineering.	16,847,000	17,729,000	16,668,000	-1,061,000
Intramural Research & Direct Operations....	6,578,000	6,578,000	6,689,000	+111,000
Positions.....	129	140	129	-11
Program Managememt.....	702,000	702,000	713,000	+11,000
Positions.....	24	24	24	-0-
Standard Level User Charge.....	76,000	76,000	100,000	+24,000
Total.....	167,614,000	187,388,000	193,435,000	+6,047,000
Positions.....	153	164	153	-11

General Statement

The National Institute of General Medical Sciences supports a broad base of research that seeks an understanding of life processes whose alteration or disturbance may lead to disease. In addition, the Institute develops and supports research programs in certain clinical specialties and on major health problems the responsibility for which lies beyond the purview of the categorical Institutes.

The Institute activities are organized and conducted through its five programs: Cellular and Molecular Basis of Disease, Genetics, Pharmacology-Toxicology, Clinical and Physiological Sciences, and Biomedical Engineering.

Since the late 1950's, this Institute had gradually developed a major program for research training at both the predoctoral and postdoctoral levels covering some 20 major discipline areas and serving future needs for trained investigators not only in the NIGMS research programs but for all of the Institutes at NIH. In January 1973, the Government began a phase out of these training grants which was interrupted a year later, but in effect, reinstated in July 1974 when the old authority was replaced by Public Law 93-348. In the summer of 1973, a postdoctoral research training program - "Weinberger Program" had been initiated offering support in a limited number of research areas judged to be in particular need of additional manpower. A similar feature of P.L. 93-348 required the Secretary, DHEW to limit support of research training to certain shortage areas. Special emphasis is given to increase the support of the MARC (Minority Access to Research Careers) training program.

Cellular and Molecular Basis of Disease

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Subactivity:				
Cellular and Molecular Basis of Disease.....	$53,956,000	$62,955,000	$64,343,000	+$1,388,000
Number.....	925	1,097	1,059	-38
Budget Mechanism:				
Research Grants:				
Regular program:				
Noncompeting.....	22,950,000	22,950,000	36,394,000	+13,444,000
Number.....	435	435	620	+185
Competing.....	7,573,000	16,572,000	5,291,000	-11,281,000
Number.....	132	304	83	-221
Subtotal,Regular.	30,523,000	39,522,000	41,685,000	+2,163,000
Number.....	567	739	703	-36
Special programs:				
Molecular Pathology Research Centers.....	488,000	488,000	425,000	-63,000
Number.....	1	1	1	-0-
Research Career....	1,922,000	1,922,000	1,773,000	-149,000
Number.....	78	78	71	-7
Scientific Evaluation.....	516,000	516,000	516,000	-0-
Number.....	---	---	---	---
Subtotal,Special.	2,926,000	2,926,000	2,714,000	-212,000
Number.....	79	79	72	-7
Fellowships.....	9,236,000	9,236,000	11,846,000	+2,610,000
Number.....	146	146	220	+74
Training Grants.....	11,271,000	11,271,000	8,098,000	-3,173,000
Number.....	133	133	64	-69
Research and Development Contracts.....	---	---	---	---
Number.....	---	---	---	---
Total.....	53,956,000	62,955,000	64,343,000	+1,388,000
Number.....	925	1,097	1,059	-38

The Cellular and Molecular Basis of Disease Program provides support through research grants, special centers, research career awards, fellowships, and training grants. The program's principal objective is to maintain a broad portfolio of research grant activities ranging from investigations on the structure of cellular water and the physical chemical properties of macromolecules and enzymes to the detailed fine-structure of cell organelles and behavior of living cells. Exceptional progress in immunology and molecular biology has led to a dynamic functional

picture of the cell that was only conjectural 20 years ago. Because of the many studies yielding significant results by some of the best scientists in the country, much of this basic research is allowed to chart its own course, but the CMBD program staff is encouraging this research to move, wherever appropriate, toward the general context of human disease. The newly developing molecular pathology centers program is designed to bring together molecular and cellular biologists with pathologists and clinical investigators in research endeavors on membranes, subcellular organelles, and studies of their altered role in disease. The ongoing program of research grants, and institutional and individual fellowships will be pursued vigorously with special emphasis on molecular pathology.

Genetics

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Subactivity:				
Genetics.....	$50,599,000	$56,733,000	$58,499,000	+$1,766,000
Number.....	830	932	902	-30
Budget Mechanism:				
Research Grants:				
Regular program:				
Noncompeting.....	29,102,000	29,102,000	38,188,000	+9,086,000
Number.....	479	479	548	+69
Competing.....	6,813,000	12,947,000	4,082,000	-8,865,000
Number.....	106	208	56	-152
Subtotal, Regular	35,915,000	42,049,000	42,270,000	+221,000
Number.....	585	687	604	-83
Special programs:				
Genetic Research Centers.....	5,768,000	5,768,000	6,500,000	+732,000
Number.....	10	10	10	-0-
Research Career...	2,299,000	2,299,000	2,305,000	+6,000
Number.....	94	94	94	-0-
Scientific Evaluation.....	---	---	---	---
Number.....	---	---	---	---
Subtotal Special	8,067,000	8,067,000	8,805,000	+738,000
Number.....	104	104	104	-0-
Fellowships.....	4,546,000	4,546,000	5,353,000	807,000
Number.....	115	115	174	+59
Training Grants.....	1,662,000	1,662,000	1,662,000	-0-
Number.....	24	24	18	-6
Research and Development Contracts.....	409,000	409,000	409,000	-0-
Number	2	2	2	-0-
Total.....	50,599,000	56,733,000	58,499,000	+1,766,000
Number.....	830	932	902	-30

In practically any important human disease or medical condition--cancer, atherosclerosis, hypertension, and mental retardation are but examples--there are genetic components. In addition, one can cite numerous purely hereditary conditions, among them sickle cell disease, cystic fibrosis, and Huntington's disease, as well as chromosome abnormalities which lead to conditions such as Down's Syndrome. Many of the adverse reactions to drugs, anesthetics, and pollutants appear to have genetic determinants. The human problems considered under the rubric of "genetics" are enormous.

The continuing primary objective of the program will be to continue to support excellent research in genetics. Among our grantees, there is a growing capability and interest in addressing the problems of human genetic disease. Advances in cellular and molecular biology, including new understanding of the structure and function of DNA, improvements in the technology of cell and tissue culture, and increased interaction between basic scientists and clinically oriented geneticists have contributed to this trend. Particular attention is being devoted to mapping of the genes on the human chromosomes, to ways of identifying asymptomatic carriers of genetic disease, and to continued support of a "library of Human Cell Lines," which makes seed stocks of well-characterized human tissue culture cells available to researchers. The latter has reduced the scientist's dependence on immediate access to patients with particular genetic conditions, which, although rare, may be particularly suitable for his studies. The following additional categories of genetic research will be emphasized:

- Basic genetic lesions--further research on the basic defects of genetic disease, most of which remain unknown.
- Molecular basis of gene action in man--studies of the effects of hormones and other substances on genes, chromosome structure, and the regulation of macromolecular synthesis.
- Multifactorial and/or polygenic diseases--predicated on the belief that understanding of single-locus gene defects can ultimately be applied to the study of these diseases.

Pharmacology-Toxicology

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Subactivity:				
Pharmacology-Toxicology	$22,329,000	$24,850,000	$25,166,000	+$316,000
Number	353	404	360	-44
Budget Mechanism:				
Research Grants:				
Regular program:				
Noncompeting	9,375,000	9,375,000	11,415,000	+2,040,000
Number	191	191	202	+11
Competing	1,838,000	4,359,000	1,450,000	-2,909,000
Number	29	80	22	-58
Subtotal, Regular	11,213,000	13,734,000	12,865,000	-869,000
Number	220	271	224	-47
Special programs:				
Pharmacology-Toxicology Research Centers	4,584,000	4,584,000	5,643,000	+1,059,000
Number	9	9	9	-0-
Research Career	626,000	626,000	630,000	+4,000
Number	24	24	25	+1
Scientific Evaluation	---	---	---	---
Number	---	---	---	---
Subtotal, Special	5,210,000	5,210,000	6,273,000	+1,063,000
Number	33	33	34	+1
Fellowships	3,090,000	3,090,000	3,590,000	+500,000
Number	64	64	83	+19
Training Grants	2,021,000	2,021,000	1,638,000	-383,000
Number	32	32	15	-17
Research and Development Contracts	333,000	333,000	333,000	-0-
Number	4	4	4	-0-
Intramural Research and Direct Operations	462,000	462,000	467,000	+5,000
Number	---	---	---	---
Total	22,329,000	24,850,000	25,166,000	+316,000
Number	353	404	360	-44

The Pharmacology-Toxicology Program embraces all aspects of drug-related research from synthesis and development of new pharmacologically active chemical structure, through elucidation of the mechanisms and sites of action of drugs, to improve the therapeutic approaches.

Among the many research areas in the Pharmacology-Toxicology Program which offer opportunities for progress, emphasis will be placed upon clinical pharmacology (with special attention to pediatric pharmacology or the use of therapeutic drugs in children), pharmacogenetics, immunopharmacology, and molecular mechanisms of toxicity. The goal of pharmacological research is to improve the effectiveness and safety of drugs. It is especially important that the final studies on the safety and effectiveness of drugs be carried out in human population by clinical pharmacologists with special training, interest, and expertise in this specific type of research. It is estimated that fewer than fifty individuals are actively engaged in investigation of the mechanisms of drug action in humans. In particular, studies of drug action in children and of the variability of such action among individuals as a result of genetic differences are areas in which progress is hampered because there are documentated shortages of well-trained scientists. The training of additional clinical pharmacologists will be encouraged and emphasized.

Immunopharmacology is becoming more important in several diverse areas of medicine. Immunosuppressive drugs are used in organ transplantation and in the treatment of several types of cancer. These drugs are extremely potent and their side effects require monitoring and control within very stringent limits. Study of immunosuppressive drugs is also leading to development of therapy for other types of diseases which appear to have their origin from defects in the immune process. These include some of the rheumatic disorders which have previously been resistant to drugs and which now show promise of management by means of drug therapy mediated immunologically.

An understanding of the mechanism by which many drugs and environmental substances exert their toxic effects is urgently needed. With the realization that many widely distributed compounds are exerting hitherto unsuspected toxic influences upon the population that may not become evident for many years, more sensitive techniques for the detection and study of these compounds have become necessary.

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Clinical and Physiological Sciences

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Subactivity:				
Clinical and Physiological Sciences.	$16,527,000	$17,765,000	$21,257,000	+$3,492,000
Number.....	186	211	231	+20
Budget Mechanism:				
Research Grants:				
Regular program:				
Noncompeting.....	2,278,000	2,278,000	5,706,000	+3,428,000
Number.....	42	42	88	+46
Competing.....	2,286,000	3,524,000	1,729,000	-1,795,000
Number.....	29	54	22	-32
Subtotal,Regular.	4,564,000	5,802,000	7,435,000	+1,633,000
Number.....	71	96	110	+14
Special programs:				
Anesthesiology Research Centers.	3,363,000	3,363,000	3,190,000	-173,000
Number.....	5	5	5	-0-
Trauma and Burn Research Centers.	2,078,000	2,078,000	4,400,000	+2,322,000
Number.....	9	9	11	+2
Research Career....	204,000	204,000	325,000	+121,000
Number.....	7	7	12	+5
Scientific Evaluation.....	---	---	---	---
Number.....	---	---	---	---
Subtotal,Special.	5,645,000	5,645,000	7,915,000	+2,270,000
Number.....	21	21	28	+7
Fellowships.....	1,042,000	1,042,000	1,678,000	+636,000
Number.....	24	24	56	+32
Training Grants.....	5,276,000	5,276,000	4,229,000	-1,047,000
Number.....	70	70	37	-33
Research and Development Contracts.....	---	---	---	---
Number.....	---	---	---	---
Total.....	16,527,000	17,765,000	21,257,000	+3,492,000
Number.....	186	211	231	+20

In addition to the current activities of this program, we plan to devote considerable effort on programming in the field of trauma and burns to encourage high quality research in these areas. The field still offers many fertile areas of investigation. A number of research opportunities have been specifically identified, such as: (1) the sequential failure of organ systems in shock, involving successively the cardiovascular, renal, pulmonary, and nervous systems;

(2) problems associated with hematologic changes, ranging from the search for blood substitutes, to the control of basic immune mechanisms; (3) wound healing, such as fibrosis and contraction, scar tissue remodeling, and successful skin grafting in burns; (4) role of the reticulo-endothelial system in trauma and burns; (5) the control of infections; and (6) behavioral aspects of severe trauma and burns.

Many of the problems of trauma need exploration in depth at the biochemical and physiologic level, and require the participation of both basic scientists and clinical investigators. This is being accomplished in the trauma and burn research centers, where such problems as metabolic disturbances, respiratory failure, fluid imbalance, and severe infections are being attacked through a multidisciplinary approach. The Institute is actively programming in the area of burns and expects to make a few more grant awards for burn research centers of high quality. The trauma and burn research program of the NIGMS is enhanced by the special interests of the National Institute of Neurological and Communicative Disorders and Stroke in head and spinal cord injury research, and of the Health Services Administration in emergency health services (e.g., developmental research, demonstration units, and emergency medical systems). These programs complement the NIGMS research program and are coordinated with it so as to facilitate the rapid translation of laboratory findings to trauma therapy.

Among promising areas for future exploration in the field of anesthesia research are studies of the molecular basis of general anesthesia; the physiologic and psychologic nature of acute and chronic pain; bioengineering approaches to safer administration of anesthetics; and development of means for instantaneous detection of hypoxia.

Biomedical Engineering

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Subactivity:				
Biomedical Engineering..	$16,847,000	$17,729,000	$16,668,000	-$1,061,000
Number.....	186	196	188	-8
Budget Mechanism:				
Research Grants:				
Regular program:				
Noncompeting.....	7,044,000	7,044,000	7,480,000	+436,000
Number	81	81	90	+9
Competing.....	2,613,000	3,495,000	1,930,000	-1,565,000
Number.....	35	45	23	-22
Subtotal, Regular.	9,657,000	10,539,000	9,410,000	-1,129,000
Number.....	116	126	113	-13
Special programs:				
Biomedical Engineering Research Centers.....	2,200,000	2,200,000	2,200,000	-0-
Number.....	5	5	5	-0-
Diagnostic Radiology Research Centers..	1,200,000	1,200,000	1,200,000	-0-
Number.....	2	2	2	-0-
Research Career.....	325,000	325,000	343,000	+18,000
Number.....	13	13	14	+1
Scientific Evaluation.....	---	---	---	---
Number	---	---	---	---
Subtotal, Special.	3,725,000	3,725,000	3,743,000	+18,000
Number.....	20	20	21	+1
Fellowships.....	484,000	484,000	764,000	+280,000
Number	16	16	29	+13
Training Grants.....	2,223,000	2,223,000	1,993,000	-230,000
Number.....	29	29	20	-9
Research and Development Contracts.....	758,000	758,000	758,000	-0-
Number.....	5	5	5	-0-
Total.....	16,847,000	17,729,000	16,668,000	-1,061,000
Number.....	186	196	188	-8

The tremendous capabilities of engineering are attested to by its indispensable role in many of mankind's most spectacular achievements, as in the applications of nuclear physics, missile development, and the development of electronic computers. It is essential now and in the next decade that a portion of our engineering resources be directed, through research and development, to the exploration and application of knowledge about life processes.

This program is concerned with the theoretical, applied and developmental aspects of biomedical engineering. Studies will be continued in the areas of biomedical instrumentation, biomaterials, patient monitoring, and computers for biomedical research. The methods and technologies of the physical sciences and engineering will be applied to the development of more effective methods for the prevention, diagnosis, and treatment of medical disorders, including the development of instrumentation and techniques in radiology and nuclear medicine to improve the accuracy of diagnosis of disease.

This program also encourages more effective use of the clinical laboratory. This depends not only on efficient analytical methods, instruments, and automated systems, but also on a better understanding of the biochemcial and physiological aspects of disease. Included is work on new and refined types of separation techniques, new modalities for the measurement of biological indicators of disease, development of more sensitive instruments and of computer hardware and software suitable for the automated analysis of biological specimens. The clinical laboratory's role in the development of more efficient approaches to diagnosis and clinical management of the sick will be explored.

Intramural Research and Direct Operations

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Subactivity:				
Intramural Research and Direct Operations....	$6,578,000	$6,654,000	$6,789,000	+$135,000
Positions.....	129	140	129	-11
Total.....	6,578,000	6,654,000	6,789,000	+135,000
Positions.....	129	140	129	-11

This activity provides professional and supporting staff required for the scientific review and administration of the 2,829 grants and 11 contracts estimated to be funded in 1976. Approximately 2,729 grants and 11 contracts would be funded in 1977.

The increase of $10,000 in personnel compensation and benefits is related to the annualization of the October 1975 pay raise. The $125,000 increase in other expenses includes an increase of $119,000 for reimbursement to the management fund for centrally furnished services, $29,000 increased costs for postage and Federal Telecommunications System offset by a decrease of $23,000 in other services.

Program Management

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Subactivity:				
Program Management....	$702,000	$702,000	$713,000	+$11,000
Positions.....	24	24	24	-0-
Total.....	702,000	702,000	713,000	+11,000
Positions.....	24	24	24	-0-

These funds provide for the support of the Institute Director and her immediate staff. They, in turn, are responsible for the overall direction, operation, planning, and development of the many Institute programs.

The increase of $5,000 in personnel compensation and benefits is for annualization of the October 1975 pay raise. The $6,000 increase in other expenses is for increased costs related to postage and Federal Telecommunications System.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$62,955,000	Indefinite	---	$64,343,000

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 projects, special centers, fellowships, and training grants.

Accomplishments in 1976: Approximately 739 regular research grants, 79 special programs, 146 fellowships, and 133 training grants will be funded in 1976. 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, 1977: 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. It is estimated that 703 regular research grants, 72 special programs, 220 fellowships, and 64 training grants would be funded in 1977.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Genetics (Public Health Service Act, Title IV, Part E)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$56,733,000	Indefinite	---	$58,499,000

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: Genetics research is supported through regular research grants, special centers, training grants, fellowships, and contracts.

Accomplishments in 1976: It is estimated 687 regular research grants, 104 special programs, 115 fellowships, 24 training grants, and 2 contracts will be supported in 1976. Much of the research in this program has broad biological significance. The concepts deriving from it will be applicable to an understanding of the construction of membranes, organelles, and viruses. In a larger, and, as yet less well-defined way, this research is expected to contribute to an understanding of the biological processes in the development of an adult organism from a fertilized egg. During the current year two new initiatives have been taken with regard to the Human Mutant Cell Bank Repository: (a) a Diabetes Cell Collection was added in order to advance the genetic analysis of this important disease; and (b) Hybrid Clone Panels for Gene Mapping to facilitate more rapid progress in the mapping of human genes. At present such mapping is only possible in a few specialized laboratories due partly to the limited supply of suitable cells.

Objectives, 1977: The following additional categories of genetic research will be emphasized: basic genetic lesions--further research on the basic defects of genetic disease, most of which remain unknown, molecular basis of gene action in man--studies of the effects of hormones and other substances on genes, chromosome structure, and the regulation of macromolecular synthesis and multifactorial and/or polygenic diseases--predicated on the belief that understanding of single-locus gene defects can ultimately be applied to the study of these diseases. Approximately 604 regular research grants, 104 special programs, 174 fellowships, 18 training grants, and 2 contracts would be funded in 1977.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$24,850,000	Indefinite	---	$25,166,000

Purpose: The Pharmacology-Toxicology Program embraces all aspects of drug-related research from synthesis and development of new pharmacologically active chemical structure, through elucidation of the mechanisms and sites of action on drugs, to improvement of therapeutic approaches.

Explanation: This program supports research through regular research grants, special centers, fellowships, training grants, and contracts. This program also funds direct training for 18 intramural NIH "research associates."

Accomplishments in 1976: Approximately 271 regular research grants, 33 special programs, 64 fellowhips, 32 training grants, and 4 contracts will be funded in 1976.

Research in the area of drug design is continuing. Selective inhibition of certain enzymes, such as proteases which are involved in the clotting of blood is being sought leading to the dissolution of dangerous blood clots. These early basic studies are promising and may provide the basis for developing new, effective therapeutic agents.

Advances continue to be made in clinical studies of new drugs and on new uses for old drugs. Lidocaine has been found to be useful in the treatment of certain cardiac arrhythmias when given intravenously. A synthetic analog of lidocaine has recently been developed which promises to have a longer half-life and to be effective orally. It has also been determined that a potent metabolite of lidocaine may be as useful as the parent drug because of its longer duration of action.

In the treatment of hypertension, the combined use of propranolol with minoxidil appears to be advantageous. Azaribine, developed in basic laboratory studies, continues to be so promising in the treatment of severe forms of psoriasis and psoriatic arthritis that, despite its toxicity, it will soon be marketed as a prescription drug.

Analytical methodology and studies on the metabolism of drugs continue to provide information which can be used to design safer and more effective dosage schedules. Such studies have led to pharmacokinetic models which help predict the most appropriate dosages, taking into account factors such as disease, age, sex, weight, plasma protein levels, and drug binding.

Objectives, 1977: Among the many research areas in the Pharmacology-Toxicology Program which offer opportunities for progress, emphasis will be placed upon clinical pharmacology (with special attention to pediatric pharmacology or the use of therapeutic drugs in children), pharmacogenetics, immunopharmacology, and molecular mechanisms of toxicity. It is estimated 224 regular research grants, 34 special programs, 83 fellowships, 15 training grants, and 4 contracts would be funded in 1977.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$17,765,000	Indefinite	---	$21,257,000

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. Trauma and burn research is directed to the discovery of better ways to prevent death from injury, mitigate pain, speed recovery of patients, and lessen the extent of disabilities caused by injuries.

Explanation: This program supports research through regular research grants, special centers, training grants, and fellowships.

Accomplishments in 1976: Approximately 96 regular research grants, 21 special programs, 24 fellowships, and 70 training grants will be funded in 1976. A better understanding of the total body response to trauma is sought. Therefore, the program fosters and encourages the coordination of basic and clinical investigations with the intent to permit a more rapid application of new knowledge gained from research in cell biology, physiology, biochemistry, pharmacology, behavioral sciences, and bioengineering.

Emphasis is also given to research on the treatment of post-traumatic infections, the nutritional requirements of convalescing victims, and rehabilitation of injured patients. Research in anesthesiology is concerned with the mode of action of inhalation anesthetics and muscle relaxants, the basic physiologic and metabolic changes resulting from anesthesia, the management of respiratory failure, obstetrical and neonatal resuscitation, handling of postoperative respiratory complications, and the pulmonary and systemic effects of drowning.

On the basis of discussions during a recent workshop on acupuncture, the NIGMS is placing special emphasis on support of research on the physiological and psychologic mechanisms of pain. The Institute is currently supporting seven research projects on acupuncture. Support is also provided for studies in epidemiology, and in behavioral sciences and adaptation.

Objectives, 1977: Continued emphasis will be placed on the afore-mentioned areas. We plan to devote considerable effort on programming in the field of trauma and burns to encourage high quality research in these areas. It is estimated that 110 regular research grants, 28 special programs, 56 fellowships, and 37 training grants would be funded in 1977.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$17,729,000	Indefinite	---	$16,668,000

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, special center grants, training grants, fellowships, and contracts.

Accomplishments in 1976: Approximately 126 regular research grants, 20 special programs, 16 fellowships, 29 training grants, and 5 contracts will be funded in 1976. Special emphasis will be given to (1) the use of the principles and practices of engineering science to explore life processes at molecular levels; (2) the application of engineering control theory for the study of physiological processes; (3) data processing for computer-aided techniques for clinical decision making; (4) microelectronic instrumentation for physiological studies and patient care; (5) the application of engineering techniques for the diagnosis and treatment of the critically ill; and (6) the use of radioisotopes, and infrared and laser radiation for the improvement of diagnostic radiology.

Objectives, 1977: It is essential now and in the next decade that a portion of our engineering resources be directed, through research and development, to the exploration and application of knowledge about life processes. Studies will be continued in the areas of biomedical instrumentation, biomaterials, patient monitoring, and computers for biomedical research. The methods and technologies of the physical sciences and engineering will be applied to the development of more effective methods for the prevention, diagnosis, and treatment of medical disorders, including the development of instrumentation and techniques in radiology and nuclear medicine to improve the accuracy of diagnosis of disease. Emphasis will be given to the initiation and development of additional Biomedical Engineering Research Centers. It is estimated 113 regular research grants, 21 special programs, 29 fellowships, 20 training grants, and 5 contracts would be funded in 1977.

NATONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: ntramural Research and Direct Operations (Public Health Service Act, Title IV, Part E)

1976 Estimate			1977		
				Budget Estimate	
Pos.	Amount		Authorization	Pos.	Amount
40	6,.54,.00		Indefinite	129	$6,789,000

Purpose: This activity provides professional and supporting staff required for guidance, surveillance, scientific direction, and administration of the individual grants operations.

Explanation: Funds are made available to provide scientific direction of grant operations and grant processing activities.

Accomplishments in 1976: This activity handles the processing of all NIGMS grants following the primary review process. In addition, it provides important aspects of program stimulation and development including scientific merit and program relevance. It is estimated 1,919 regular research grants, 257 special programs, 62 fellowships, 188 training grants, and 11 contracts will be funded in 1976.

Objectives for 1977: The staff would continue to provide close surveillance over the many NIGMS grants. Approximately 1,754 regular research grants, 259 special programs, 162 fellowships, 154 training grants, and 11 contracts would be funded in 1977.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Program Purpose and Accomplishments

Activity: Program Management (Public Health Service Act, Title IV, Part E)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
24	$702,000	Indefinite	24	$713,000

Purpose: Program Management provides for the overall leadership and staffing necessary for the administration and management of the research effort of the Institute.

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, operation, planning, and development of the many Institute programs.

Accomplishments in 1976: The Director and supporting professional and clerical staff provide continuing guidance and surveillance over the many programs of the Institute.

Objectives for 1977: Continued leadership will be provided for the administration and management of these programs.

National Institute of General Medical Sciences

Transition Quarter Analysis

Budget Authority by Activity

	1976 Estimate	Transition Quarter
Cellular and Molecular Basis of Disease	$62,955,000	$10,919,000
Genetics	56,733,000	12,497,000
Pharmacology-Toxicology	24,850,000	6,032,000
Clinical and Physiological Sciences	17,765,000	4,525,000
Biomedical Engineering	17,729,000	4,705,000
Intramural Research and Direct Operations	6,578,000	1,439,000
Program Management	702,000	158,000
Standard Level Users Charge	76,000	20,000
Total	ł87,388,000	40,295,000

Explanation: The requirements for the transition quarter reflect the necessary funds to honor commitments for research grants, special centers, fellowships, and contracts. In accordance with present policy for this period, some competing awards will be made.

The amount in Research Management and Program Services is required for the direct operations of the Institute for the three month period.

FEBRUARY 26, 1976.

NATIONAL HEART AND LUNG INSTITUTE

WITNESSES

DR. ROBERT I. LEVY, DIRECTOR
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT L. RINGLER, DEPUTY DIRECTOR, NATIONAL HEART AND LUNG INSTITUTE
EVELYN L. ATTIX, 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
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. NATCHER. We take up next the National Heart and Lung Institute.

We have before the committee Dr. Robert I. Levy, the Director of the National Heart and Lung Institute. Doctor, who do you have with you?

Dr. LEVY. I have with me Dr. Robert Ringler, the Deputy Director of the Institute. I have with me for the first time Evelyn L. Attix, our new Executive Officer, and Mr. John Reeder, our Financial Management Officer, as well.

Mr. NATCHER. We are delighted to have all of you at this time. Would you like to place your statement in the record in its entirety and highlight it for us, or would you like to read it?

Dr. LEVY. I would be pleased to place it in the record and highlight it.

Mr. NATCHER. That would help us. We will also place your biographical sketch in the record at this point.

[The material follows:]

Name: Robert I. Levy, M.D.
Position: Director, National Heart and Lung Institute.
Birthplace and date: Bronx, N.Y., May 3, 1937.
Education: June 1953, graduated from Bronx High School of Science; 1957, B.A., Cornell University, highest honors and distinction in Zoology; 1961, M.D., Yale University, cum laude.
Experience: 1975 to present: Director, National Heart and Lung Institute.
1973–75: Director, Division of Heart and Vascular Diseases.
1970–74: Chief, Lipid Metabolism Branch, National Heart and Lung Institute.
1969–73: Chief, Clinical Service, Molecular Disease Branch, National Heart and Lung Institute.
1966 to present: Head, Section on Lipoprotein Metabolism and Intervention, Molecular Disease Branch, National Heart and Lung Institute.
1966–68: Attending physician, Georgetown University Medical Division, District of Columbia General Hospital, Washington, D.C.
1965 to present: Attending physician, Molecular Disease Branch, National Heart and Lung Institute.
1965–66: Chief Resident, National Heart and Lung Institute.
1963–66: Clinical Associate, Section on Molecular Diseases, National Heart and Lung Institute.

1962–63: Assistant resident in medicine, Yale-New Haven Medical Center.
1961–62: Intern in medicine, Yale-New Haven Medical Center, New Haven.
Association memberships: American Society for Clinical Investigation, American Institute of Nutrition, American Federation for Clinical Research, American Heart Association Council on Arteriosclerosis, New York Academy of Sciences, American Society for Clinical Nutrition, American College of Cardiology, American Society for Clinical Pharmacology and Therapeutics.
Special awards, citations, or publications: Kees Prize Research Thesis, Yale University, 1961; Alpha Epsilon Delta (premedical); Alpha Omega Alpha; Phi Beta Kappa; Phi Kappa Phi; Sigma Xi; Arthur S. Flemming Award, 1975; DHEW Superior Service Award, 1975; Author or coauthor of approximately 150 publications; Editorial board—Journal of Lipid Research, Circulation and Dialogues in Nutrition.

OPENING STATEMENT

Mr. Chairman and members of the committee, it is a particular pleasure for me to be here today. As you know, I have only recently assumed my present position as Director of the Institute, and this is my first opportunity to appear before you in that capacity.

Both the Institute and our Advisory Council have forwarded the annually updated reports on the national heart, blood vessel, lung, and blood program as required by the Congress. I would like to summarize, just as few of the accomplishments of our legislated national program since we last reported to you.

First let me say that it is difficult to overemphasize the magnitude of the disease problems for which the program and hence the Institute has responsibility. Measured in terms of illness and disability there are over 30 million Americans with cardiovascular, pulmonary, and blood disorders. Cardiovascular diseases alone account for over half of all deaths in the United States with coronary heart disease, the major killer, resulting in nearly 700,000 deaths. In economic terms, figures just released and based on 1972 data reveal that heart, lung, and blood diseases cost the Nation some $58 billion annually, nearly one-third of the total cost of disease and illness in the United States. The dollar cost to the Nation of premature coronary death, primarily in the young and middle aged male population, alone amounts to over $22 billion a year. I can report, however, that we are making progress. After nearly two decades during which deaths and the amount of illness from heart and lung diseases were steadily increasing we have now turned the corner and for the past 7 years there has been a slow but steady decline in both mortality and morbidity statistics for these diseases. As one example, the age-adjusted death rate for coronary heart disease in 1973 was some 10 percent less than it was in 1968. However, the fact remains, as I said previously, that an unduely large percentage of our population continues to die from heart diseases. The fact that many of these deaths are considered to be premature emphasizes the importance of prevention programs.

The progress that has been made in reducing these dreadful statistics has come about for many reasons. They include better understanding of disease processes, and hence an improved ability to diagnose them earlier and with greater precision, as well as improved treatment modalities. Perhaps, however, of greater importance is the new knowledge that has been gained to prevent disease in the first place.

Passage of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 gave the Institute several new mandates, some of which I will speak about later. Perhaps one of the most important was in the area of disease prevention. We are pursuing it vigorously on several fronts. Again, I will highlight some of the specifics later in my statement.

HEART AND BLOOD VESSEL DISEASES

Now I would like to summarize a few recent accomplishments in the area of heart and blood vessel diseases.

Each year in this country over 300,000 deaths occur from what is called sudden cardiac death, that is, death within 6 hours from onset of acute symptoms. The majority of these deaths occur before the individual reaches the hospital or other medical attention.

The Institute has been pursuing a vigorous effort in this area for several years. It is beginning to pay off. We now know that the overwhelming majority of these sudden cardiac deaths occur because of an irregularity in heart rhythm. We also know how to correct the irregularity in heart rhythm. Therefore, if the individual can be reached in time, death can be prevented in a large percentage of cases. In certain emergency care systems, largely because of these new techniques

concerning heart rhythm, as many as two-thirds of heart attack victims who are afforded medical care in time walk out of the hospital.

Obviously a solution to the problem of sudden cardiac death will require more research that will enable us to learn how to identify individuals at high risk and find better means of preventing the irregular rhythm in the first place. Efforts in both of these areas are being pursued.

Exciting progress is being made in reducing damage to the heart itself following a heart attack. We now know that the amount of damage to the heart muscle at the time of a heart attack is not fixed but hangs in the balance from several hours to as much as a few days. The extent of this damage to the heart muscle can now be determined by measuring certain enzymes in the blood, by a special kind of electrocardiogram, and by using certain radioactive isotopes that are selectively attracted to either the damaged or the normal part of the heart muscle. The ability to measure the extent of damage to the heart following a heart attack, and the knowledge that it may be minimized enables us to direct our attention to finding improved methods for controlling the size of the injury and hence the extent of permanent damage to the heart itself. Progress is being made here, and we anticipate undertaking clinical trials in determining and minimizing heart muscle damage within the next couple of years.

We can report progress in the development of noninvasive diagnostic techniques like echocardiography—ultrasound—and computer-based X-ray image intensification to harmlessly and noninvasively measure the extent of cardiac and blood vessel disease both before and after clinical symptoms appear. Such new techniques are now being used selectively in several hospitals and clinics across the United States and our intramural cardiology group has a very active research program underway. These techniques are allowing the cardiologist to detect the early stages of disease often long before clinical signs develop, when changes are still hopefully reversible. They will also simplify future clinical trials by allowing us to telescope these trials in time, size, and cost.

In this regard, I am pleased to report to you that two of the Institute's most ambitious and costly clinical trials aimed at testing the concept of primary prevention of coronary heart disease through risk factor intervention, the lipid research clinic coronary prevention trial and the multirisk factor intervention trial, have just completed their patient recruitment phase. They have enrolled over 4,000 and 12,000 patients respectively during the last 2 years after screening 1 million individuals. Another multicenter clinical trial, to test at which level of blood pressure treatment should begin, is entering its third followup year. Another to see if regular aspirin ingestion can reduce the heart attack rate, and a fifth to assess in detail the indications for and the long-term effects of coronary artery surgery are still recruiting and randomizing patients but are on target.

We have also learned the secret of how specific proteins can carry lipids—fat—in the blood and how the blood platelets and the arterial wall interact with these lipid protein complexes. This will have significant future consequences. Furthermore, it has now been conclusively demonstrated in nonhuman primates that not only can the arteriosclerotic process be controlled with the use of specific low-cholesterol diets and drugs, but that regression and reversal of existent arteriosclerosis may occur. Though these rigorously performed studies using animal models of human arteriosclerosis cannot be performed in man, our human clinical trials will hopefully give us similar information about disease prevention within the next decade.

In hypertension we continue to search for the basic processes that lead to high blood pressure and continue to evaluate new forms of potential therapy. In high blood pressure, in contrast to arteriosclerosis, we already have conclusive evidence from completed clinical trials that currently available forms of drug therapy not only normalize blood pressure in man but prevent strokes, renal failure, and heart failure. Thus, we have enthusiastically launched and are coordinating the national high blood pressure education program in partnership with other governmental and voluntary agencies. I am delighted to report today that the program, our first large effort in public and professional education, appears to be a great success.

When the program was launched in 1972, we estimated that there were about 23 million Americans with high blood pressure. It was also believed that only about 12 to 15 percent of them were under optimal medical treatment. In the 3 years since the program began the number of patient visits to physicians for hypertension has increased by over 40 percent. New patients seeking treatment for hypertension alone have increased by over 28 percent. The number of Americans

unaware of their hypertension appears to have been reduced by almost 5 million and the number of subjects under effective blood pressure control appears to have doubled to almost 8 million. Though these results are most satisfying more must be done. There are still over 7 million Americans unaware of their high blood pressure, and an even larger number aware but not yet on effective therapy. It is clear that our further education efforts must be linked with efforts in the behavioral sciences if we are going to help these patients assume responsibility for their own health.

LUNG DISEASES

Our lung program also covers the continuum from basic to applied research and the translation of results into practice. However, by design, much of the emphasis continues to be on basic research. Priority has properly gone to acquiring detailed new information on the structure of the lung, the type of cells that make it up, the functions of the lung other than breathing, the nature composition, and function of lung secretions, and the causes and mechanisms of diseases of the lung. These findings are laying the needed foundation for clinical advances in the future. There are, however, areas of clinical promise that are actively being explored today. These include clinical trials in the early detection and treatment of respiratory distress in the newborn infant and the early detection and treatment of acute respiratory failure in adults as well as children.

The recognition of the magnitude of the health problem produced by chronic bronchitis and pulmonary emphysema in this country has led to mounting interest in their underlying causes and natural history as well as their early detection, prevention, and treatment. These disorders have some underlying similarities hence they are commonly grouped together and referred to as chronic obstructive lung disease. Intensive research efforts supported by the Institute are providing promising clues to the causes of chronic obstructive disease in the lung and to the mechanisms by which this group of diseases develops.

It has only been a decade since a specific hereditary enzyme defect in alpha$_1$ antitrypsin was shown to be associated with one form of emphysema. This discovery gave an entirely new dimension to the understanding of emphysema and lung biology in general. Current research is designed to reveal the precise role of this defect in the overall problem of chronic obstructive pulmonary disease. Still more exciting is the fact that investigators are beginning to define the role of other enzymes in the onset of emphysema, studies that may provide a basis for the prevention of the disease.

A combination of noninvasive pulmonary function tests are now believed to localize the basic obstructive defects in emphysema and bronchitis and thus make it possible to assess progression of these diseases. Validation of these tests would show great promise for they open the possibility to interventions that could prevent or arrest obstructive lung disease.

A new and more direct approach now permits X-ray visualization of minute areas of the lung by means of microfocal spot magnification. This technique, recently developed by pulmonary researchers, will provide further insight into the basic changes that occur in patients with chronic obstructive lung disease. It might also lead to more accurate diagnosis of other pulmonary diseases including black lung.

Studies in animals with a disorder that is analogous to chronic obstructive human lung disease have demonstrated that progression of the disease can be showed, if not completely arrested, by elimination of such casual agents as smoking. If these data are confirmed in patients there is reason to hope that human disease can also be arrested before the patient is totally incapacitated and thus very difficult to treat.

BLOOD DISEASES AND BLOOD RESOURCES

Our blood program has supported a great deal of basic research and clinical activity in the area of sickle cell anemia and the other hemoglobin disorders. We have learned a great deal about hemoglobin synthesis and what goes wrong in the actual molecular defect in some hereditary blood diseases. We have learned, for example, that in some diseases there is an absence of a gene responsible for hemoglobin synthesis, in others there is a defective gene which produces a defective product, and in still others a defective gene which can produce no product at all. In Cooley's anemia, for example, we have learned that the molecular defect appears to be faulty regulation of the synthesis of the gene product. In other words, the gene is defective.

The nature of the missing clotting factors in the various forms of hemophilia are being studied, and their effects are better understood. It has become clear that in a significant number of hemophiliacs the abnormal development of so-called inhibitors prevents the usual treatment with antihemophilic factor—factor VIII—from being effective. A cooperative study in 10 clinical centers is investigating the natural history, causation, and, hopefully, the eventual prevention or treatment of these inhibitor effects.

The obverse of problems associated with bleeding is the problem of clotting with the resultant occlusion of blood vessels in, for example, the legs, the lungs, the head. A new approach that offers considerable promise in the prevention of postoperative thrombosis, or blood clot formation, is the use of small amounts of heparin, an anticlotting agent. Pulmonary embolism, clots in the blood vessels in the lungs, is a fatal complication of surgery in an estimated 5,000 to 10,000 patients per year. Such emboli arise from clots that usually form in the legs and pelvic veins. Recent studies have demonstrated that the development of such clots can be markedly inhibited by administration of low doses of heparin before, during, and after surgery.

Our program is also concerned with research in blood resources. Many patients are being treated in part by transfusion of blood products such as platelets for the cancer patient, factor VIII for hemophiliacs, albumin for the burn patient, and red blood cells for those that are anemic. The availability of these products, their cost, and their safety are of major concern to the Nation. Considerable research effort is aimed at assuring availability of safe blood and products to those in need. For example, frozen red blood cells can now be stored almost indefinitely and constitute an important resource, although they are very perishable after thawing. A study designed to extend the storage life after thawing and thereby the wastage due to outdating is nearing completion. Sterile connecting devices have been developed which will allow the transfer of blood and other fluids to be made in a closed system thereby preventing contamination and vastly extending the useful life of red blood cells after thawing.

One more thing before I conclude, Mr. Chairman, I would speak to the issue of basic, nontargeted, investigator-initiated, biomedical research. While the Institute is committed to the full continuum of effort called for by the Congress, including clinical investigation and the translation and dissemination of research results to the person in need, the primary means for prevention will evolve from basic research. Research is very difficult work, one of man's most frustrating professions. More often than not, large blocks of an investigator's career must be invested to provide the basis for a single advance. Many blind alleys have to be explored by numerous scientists so that another may make a discovery. Decades may be needed to follow an elusive clue to find out if it is leading to an answer that will help cure disease. Because of those bright ideas which occur to scientists sometimes only after many hard years of work, people live where before they died.

In conclusion, Mr. Chairman, the budget request for the National Heart and Lung Institute for 1977 is $342,855,000. I shall be pleased to answer any questions and supply additional information desired for the record.

Dr. LEVY. Let me first say it is a pleasure to be here for the first time, and since this is the first time, I would like to reaffirm my own and my Institute's commitment to the full biomedical research spectrum as we think of it from basic research through clinical research and clinical trials to education and demonstration activities, all aimed ultimately at the primary or secondary prevention of cardiovascular, pulmonary, and blood diseases.

MORBIDITY AND MORTALITY

I don't think it is really necessary to talk about and it is very difficult to overemphasize the magnitude of the disease problems for which our Institute has responsibility. Measured in terms of illness and disability there are over 30 million Americans with cardiovascular, pulmonary, and blood diseases. Cardiovascular disease alone accounts for over half the deaths in the United States. In economic terms these disorders cost the Nation over $58 billion each year.

Despite these dreadful figures there are signs that we are very pleased and proud of. Especially that the major killer, coronary heart disease, has been declining as a cause of death. In my prepared statement I say there was a 10-percent decline from 1968 to 1973. I am pleased to say that we have information now in 1975 showing there has been a further 4.6 percent decline in coronary heart disease mortality in the last 2 years. What this means in simple terms is that in both 1974 and 1975 30,000 less Americans each year died of heart attack than had previously.

SUDDEN CARDIAC DEATH

I would like to emphasize just a few of the recent accomplishments that we are proud of. I would like to begin with sudden cardiac death. This is death that occurs suddenly. We usually define it in terms of a few hours to 6 hours from the onset of the final event. It is a major cause of death. Of the coronary patients, 300,000 to 400,000 die this way each year. Of even more concern, one out of every four Americans has as his or her first sign of coronary heart attack sudden death, clear information that we can't wait until vascular disease manifests itself but have to strive for prevention.

In terms of sudden death, we have been able to define a number of risk factors in the last several years that indicate a subject is more likely to die suddenly. This has to do with detection of irregular rhythms in the heart, as well as other factors, factors that we have identified as risks for coronory disease itself.

Smoking and high blood pressure are two of the major factors that put a person at increased risk for sudden death. The diabetic is at great increased risk for sudden death. We know that most of the sudden deaths occur as a result of a disturbance in heart rhythm. We have a large number of drugs that can control this abnormal heart rhythm. In the next several years we hope to evaluate these drugs, and in this regard I might say that this evaluation is possible now only because there are low-cost monitoring devices that allow us to monitor heart rhythm, not while at a doctor's office but for a patient 24 to 48 hours at a time as a patient wears a simple device.

PATIENT MANAGEMENT

Another exciting area that perhaps was not a scientific area of study in the past deals with the management of patients who have had heart attacks. We used to think that a heart attack was the last phase of an event. We now know that the heart attack begins an event in which heart muscle damage is progressing until eventually the heart muscle dies. We know this event occurs not over minutes but over hours to days. We have to measure the size of damage to the heart now. These are enzyme techniques. These are electrode placement techniques. These are radio isotope techniques where the isotope will go to the abnormal or normal portions of the heart. Using these techniques, we can for the first time put sense into what was nonsense before and test old wives tales, such as the value of giving nasal oxygen or lying in a particular position. We now can test all of these tales, and it turns out many of the old techniques, including the use

of oxygen, are beneficial. The use of nasal oxygen will decrease the amount of heart muscle damage that will occur. We can also evaluate new techniques, the use of anti-inflammatory agents which decreases inflammation.

It has been shown in animals and now most recently in man that the drug decreases the amount of heart muscle damage that occurs in a heart attack. We are very excited about this because it gives us the opportunity to make the management of a patient with a heart attack scientific. We can evaluate different forms of drugs, devise therapy, and are able to monitor what we have done to the patient. The importance of this really resides in the fact that now that we can handle rhythm problems that occur in the coronary care unit which used to be a major cause of death. The major problem in a coronary care unit is what we call pump failure. If we can truly reduce the size of each heart attack, we can decrease this failure of the heart itself.

We hope to begin this year some clinical trials to evaluate not only the acute effects of decreasing heart attack size but the long-term effects. Will the patient's heart be able to function better 6 months after he has been treated wtih these new heart attack-reducing drugs? Will the patient have a better life? Will the morbidity and mortality after a heart attack decline?

NONINVASIVE DIAGNOSTIC TECHNIQUES

I would just mention in passing that we are very pleased with the developments of noninvasive diagnostic techniques. It has been a major emphasis of the Institute since 1974. Arteriosclerosis is a totally secret disease. We have publicized hypertension for the last several years as a silent disease but arteriosclerosis begins in the first decade and runs for as many as seven decades, often before it manifests sometimes as a first sign with sudden death. We have sought methods to detect the progression of arteriosclerosis before it manifests itself using some of the sonar techniques that were developed in the Navy, and other techniques such as ultrasound. We can get some inkling about the amount of arteriosclerosis in large vessels in the neck and legs, about the function of the heart and its valves without exposing the patients to risk of catheterization or other procedures. Those techniques 3 or 4 years ago were techniques we would describe as being experimental.

They are now being used in many laboratories, in many clinical facilities around the country, and if you can imagine, Mr. Chairman, the amount of money that can be saved by evaluating an infant's heart using an echo technique which merely requires that a small device be placed in and around over the heart and chest, as compared to the past when we would have to hospitalize the child for 1 to 3 days, catheterize the child, and expose the child to risk; the savings in time and in costs are enormous and the promise of these techniques for the future is very great.

RISK FACTORS

I am pleased, leaving this subject of coronary heart disease for the moment, to talk about one of our major goals in prevention, which has been to focus on the risk factors, factors that suggest that an individual

is at increased risk for heart disease—factors like high blood pressure, high cholestrol, high amounts of fats in the blood. We have talked about clinical trials that we were going to begin and were in motion. I am pleased to report that we have now completed recruitment for the two largest of these clinical trials, the lipid research clinic coronary prevention trial, and the multirisk factor intervention trial. We have recruited 4,000 and 12,000 subjects respectively over the last 2 years. This has involved screening some 1 million Americans.

Several other clinical trials are in progress. They include the evaluation of the most effective level of blood pressure to treat; the evaluation of aspirin as a preventive or protective agent in patients who have had heart attacks to prevent another; and the evaluation of coronary artery bypass surgery, which is now being done at a rate of some 40,000 to 60,000 procedures a year. I hope that we will be able to talk more about these trials in the future.

CHOLESTEROL

On the basic level, when it comes to arteriosclerosis I am delighted to report that we now understand how cholesterol and other blood fats circulate in the plasma. We know there are specific proteins that can carry this fat, and, what is new now, is that we understand how these proteins carry the fat, how the basic amino acid structure of these proteins makes them a vehicle for the transport of the fat—exciting because we can now synthesize proteins building on the same kind of protein structures, and ultimately we would like to think that we can infuse synthetic proteins that may act eventually, perhaps not in this decade, as chemical roto-rooters that might remove lipid from already existing deposits.

In the latter regard I am delighted to report that 4 or 5 years ago if we came to this committee we talked about our hope that through risk factor we could slow arteriosclerosis or prevent it from getting worse. We now have conclusive evidence from four different groups of investigators that in nonhuman primates, monkeys, not only can one prevent progression of arteriosclerosis produced by diet, high cholesterol, or other factors, but one can actually demonstrate regression with intervention, with changing of diets and drugs—that is the arteriosclerosis disappears.

It is delightful to think that a process which is responsible for so much death and disability can actually be regressed and made to go away.

NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM

Before leaving the cardiovascular field, I have to highlight one last area that we are most proud of and that is our national high blood pressure education program.

As you know, in contrast to arteriosclerosis in which we are not clear or sure that we have definite effective means of therapy, in hypertension, though we don't know all the basic causes, we do have effective information from clinical trials that have already been done that treating blood pressure will decrease heart failure, renal failure, and stroke.

That was the reason for beginning the high blood pressure education program. There were 23 million Americans with high blood pressure. Less than one-half of them knew that they had high blood pressure. Less than one-eighth of them were on effective treatment. The program began some 3 years ago, a program coordinated by the Institute but involving all other Federal agencies and voluntary groups as well. It has been, as measured by things we can measure, a great success.

We have information that tells us that in the last 3 years the number of patient visits for hypertension have increased by better than 45 percent. The number of new patient visits for hypertension have increased by 38 percent. Of more importance, surveys have been done in 14 communities that can be compared to the original surveys that showed us how little the public knew about this disorder. These surveys suggest that there are now some 5 million more Americans who are aware of the disorder than were before and, perhaps of most importance, there are some 4 million more Americans, double the number just a few years ago, who are now on effective therapy for high blood pressure. This isn't good enough.

This disorder is found in 23 million Americans. There are some 6 million who don't know they have it. There are almost 7 million who know they have the disorder who aren't under effective therapy. In this regard we are working with the behaviorists to try to find ways to help the patient help himself, take care of his disorder, follow through on drugs and diet.

LUNG RESEARCH

In the lung area we again emphasize the whole spectrum from basic to applied research through translation but by design we have focused a good deal of attention on basic research, on the structure of the lung, on the nature of the cells, how the lung breathes, the metabolism of the lung. These fundamental studies receive particular emphasis as they provide an understanding of disease processes that underlie many, and in some instances all, of the categorical pulmonary diseases that are addressed by the Institute. These diseases range from pediatric pulmonary diseases, of which hyaline membrane disease is the most common cause of death in the newborn, to respiratory failure, which may occur from many different metabolic disorders. Pulmonary vascular diseases, fibrotic and immunologic diseases of the lung, and chronic brochitis, and emphysema are among other disease categories which are receiving particular attention by the Institute.

This year, the pulmonary program is engaging in two clinical trials. One trial is evaluating the efficacy of antenatal corticosteroid therapy in prevention of neonatal respiratory distress syndrome. The centers participating in the study will collect data to determine if the therapy has any adverse effects on the mother, as well as data on morbidity and mortality of the infant with respiratory distress syndrome. The second study will evaluate the efficacy of long-term intermittent positive pressure breathing treatment when used as an adjunct to the overall care of ambulatory patients with chronic obstructive pulmonary disease.

We have learned a tremendous amount. We have improved our methods to diagnose chronic obstructive lung disease, chronic bron-

obits, and emphysema. We have learned, through a lead made possible by the discovery of a genetic disorder in which an enzyme is deficient, that the amounts of the enzymes breaking down elastin and collagen in the lung have a tremendous effect on whether people develop emphysema and chronic bronchitis.

BLOOD RESEARCH

In the blood area we continue to do basic work on the molecular diseases including sickle-cell disease. We learned, as you recall, in this past 8 months that in Cooley's anemia the problem lies in the production of a faulty materials so that not enough of a specific portion of hemoglobin, the Beta chain, is made, and therefore these patients have too much of one portion of the hemaglobin and get into all sorts of problems with red cell division.

In sickle-cell disease, as you know, a faulty material is made, a material that differs in one amino acid but produces tremendous abnormalities.

In hemophilia we have started this last year a study to evaluate the efficacy of treatment in the hemophiliac, looking at the fact whether the inhibitors in hemophiliacs who receive large amounts of antihemaphiliac factor—what effect they have on the disease. Do they lead to an increased requirement for antihemophiliac factor? Do they change the pattern and nature of the disease?

This study has just been begun. The obverse of bleeding is clotting, and I am pleased to report in terms of a breakthrough clinically that it has been demonstrated now that the use of minidoses of anticoagulant agent, Heparin, can protect patients from postoperative pulmonary emoblism, the breaking off of clots in the legs and other vessels which lodge in the lungs or more severely sometimes in the brain and other places.

It has been demonstrated very nicely that giving the minidose of Heparin during the operation and before does not affect clotting in terms of the patient bleeding but has a dramatic effect in terms of reducing the incidence of pulmonary embolism.

BLOOD RESOURCES

Perhaps as a last item to highlight, as you know, we are about to become the Heart, Lung, and Blood Institute and are very aware of our responsibilities in not only blood but blood resources.

Our program is concerned with all of the blood product such as platelets for the cancer patient, factor 8 for hemophiliacs, albumen for burn patients, and red blood cells for those who are anemic. The availability of these products, their cost, and their safety are of major concern to the Nation. Considerable research has been going on to make the blood safe and readily available. We are now sponsoring a study to look at the efficacy of preventing hepatitis by washing red blood cells.

It has been known that washed frozen red cells are not associated with hepatitis risk. The simple question as to whether it was the washing or freezing that protected patients from hepatitis was not asked.

It is being asked now, and if the simple washing of red blood cells can protect a patient from hepatitis, it will be a major boon.

I would also say in this regard because I know the chairman and the committee are interested in inexpensive methods, that we have served as the prime movers in the development of a simple transfer device so that one can enter closed blood units and remove samples for different purposes as many times as one would want. The old rules were that once a blood bag was opened, the blood had to be discarded in 24 hours. A simple development of two different types of plastic that melt into each other with a warm iron allows us to go from one to another connector. It is estimated by the developers this will be marketed for less than 10 cents a connector. It will save enormously.

As the chairman and the committee probably know, a large amount of our blood is unfortunately discarded because of the present rules in opening and closing of units. This is a very simple technique that will make possible tremendous savings.

In conclusion then, Mr. Chairman, the budget request for the National Heart and Lung Institute for 1977 is $342,855,000. I shall be pleased to answer any questions and supply additional information desired for the record.

Mr. FLOOD. How long have you been on board?

Dr. LEVY. Since September, Mr. Chairman.

Mr. FLOOD. I think the records will show that you are not new at the NIH. How long have you been identified with the NIH and with the sister institutes?

Dr. LEVY. I have had the privilege of being with the National Heart and Lung Institute since 1963. I came first as a clinical associate and spent my first 10 years working primarily in the research laboratory studying lipid metabolism and arteriosclerosis.

Mr. FLOOD. You also were in New Orleans when I was there at the American College of Cardiology Convention. I was amazed to be advised there were over 8,000 cardiologists registered at that convention. I understand there were others who didn't register. This just shows the concern with the problem and the attention it is receiving.

BUDGET IMPACT

The 1977 budget for the Heart Institute is $27,482,000 below the 1976 appropriation. What is the impact of that reduction? Spell out in what areas this impact is going to be felt.

Dr. LEVY. Mr. Chairman, let me first say that this budget of $342,855,000 was developed from a different base on the assumption that our budget for fiscal 1976 would be the President's budget, which was $293 million.

Taking on the commitments and activities, several recommended to us by this committee associated with our recently approved 1976 budget, changes the picture, so that at the budget level of $342,855,000, we find ourselves in an extremely embarrassing position.

What it means is no program expansion, no new initiatives, and, perhaps more concerning, Mr. Chairman, it means a dramatic phaseout in our training program that we consider vital.

It means a program reduction. The only place we can really make changes, Mr. Chairman, and not affect ongoing programs, is in the competing and new grants. It means a dramatic reduction in the number of competing and new research grants we will be able to award.

You see a figure in the budget for competing the new grants of about $23 million. Many of those dollars are at least tentatively earmarked for the competitive continuation of the specialized centers of research that this committee first earmarked back in 1971.

In 1971 specialized centers of research in arteriosclerosis and pulmonary disease were begun to look at both basic and clinical research. It has been 5 years now.

The centers were guaranteed funding for 5 years, and in the original memo we talked about a competitive renewal. We are holding the competitive renewal now. We have gotten some 50 applications requesting some $66 million of first-year funds.

Our hope is to be able to at least continue the pulmonary and arteriosclerosis program at its present level. If we do that, that comes out of the competing line. We will have less than $6 million left for any other new and competing grants. Mr. Chairman, it is easy to calculate that would allow us to fund some 4 percent of new and competing research grants.

Mr. FLOOD. Then you have an impact which is pretty widely spread.

Dr. LEVY. Yes, Mr. Chairman, in fact, what we have chosen not to do is to lop off any major program. Most of these programs have been begun in the last 4 years and we have chosen at least at the present time to estimate the reduction so that all of our programs suffer.

The programs in heart, lung, and blood and all of the subprogram areas like arteriosclerosis and coronary heart disease in this justification take a percentage reduction.

NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM

Mr. FLOOD. Last year we talked about the national high blood pressure education program. How much are you going to spend in this particular program in 1976 and what are your plans for the program in 1977?

Dr. LEVY. In 1976 the total expenditure for the program will be somewhere close to $3 million. We are very proud of this program because by working with other agencies and the voluntary sector we get many millions of dollars more out of it.

This program and other elements it supports, like educational research grants that aren't included in the $3 million, will take a percentage reduction.

Mr. FLOOD. What are your plans for 1977?

Dr. LEVY. Right now we just applied a percentage and the program will fall by somewhere around $400,000, Mr. Chairman.

Mr. FLOOD. We were also told about a hundred National, State, and local organizations involved in this same program. Have you been able to involve any additional organizations in this?

Dr. LEVY. The mention of 100 has to do primarily with "High Blood Pressure Month," a joint venture of local, State, and voluntary groups. The first High Blood Presure Month, which was May, 2 years ago, involved a little less than 100. Last year's involved over 130 different groups in over 900 communities.

The program also works year round with many, but not all these groups, as a result of relationships established in preparing for High Blood Pressure Month. This is because we see the month as a means to

initiate involvement over the long term, not for just a brief 30-day period.

Mr. FLOOD. Have you involved any additional organizations?

Dr. LEVY. We expect to have many more groups involved this year. Certainly the number of communities involved will be well over 1,000. Because we are more successful in having groups report activities they have accomplished, rather than sharing their plans in advance, it is difficult to make a realistic estimate at this time.

Mr. FLOOD. Last year you people also told us the Heart Institute offers—let me quote—a "Community Consultation Service." There are over 300 communities that take advantage of the service. Do you plan to continue to offer this service in 1977, and how many additional communities will you serve?

Dr. LEVY. We have had an increasing number of requests from communities who would like to start up programs to help their communities help themselves. We are averaging about 25 to 30 contacts per month. Some require only instructional materials, but many need extensive technical assistance. The latter is placing a severe strain on our existing personnel who can stretch the physical presence only so far. It is not clear that we will be able to expand this portion of the program in 1977 at the present budget level—despite the fact that we provide no direct support of community activities, but insist that local resources be used.

Mr. FLOOD. Since we talked about it, what kind of community agencies are involved in this high blood pressure program?

Dr. LEVY. Many different groups ranging from local voluntary agencies, to service clubs, to employee health programs, to local and State health departments or private health departments or medical groups or women auxiliaries who learn about high blood pressure, think it is a good thing to do something about and can make a contribution.

What we have to do then is try to motivate these groups to coordinate or coalesce their efforts, to integrate their activities with those of existing medical facilities. A well-meaning screening program that doesn't measure blood pressure accurately or which just measures blood pressure, but does not try to assure that the patient gets under care, is not effective in achieving blood pressure control.

Mr. FLOOD. That is why I wanted a list of what happened.

Do these local community organizations or agencies have the capability to screen patients for high blood pressure?

Dr. LEVY. What we try to do is serve as midwives and get the auxiliary group that can provide some of the person power together with a local medical or nursing group so that a total community focus can do the job. There are many resources in every community. We see our own role as one of bringing these resources together and mobilizing them to produce a sum which is greater than the parts.

Mr. FLOOD. How many people are screened on an annual basis?

Dr. LEVY. We are pleased to say we now know from our own nationwide surveys that 5 million more Americans are aware they have high blood pressure now than they did in 1971; that some 4 million more Americans are under effective blood pressure control. That is double the number that existed in 1971. Both total patient visits and first visits to physicians for hypertension and hypertensive heart disease have risen by at least one-third in the same time period.

Mr. FLOOD. Doctor, one of the problems in treating the hypertensive patient, whoever it may be, is this matter of medication. In the first place it's expensive and very frequently it has very unpleasant side-effects of all kinds. The result is that many patients will not be part of it, they rebel. They simply refuse to take the medication. Are you conducting any kind of research to improve this drug therapy program?

Dr. LEVY. Yes, Mr. Chairman. As part of our overall national high blood pressure program we have a high blood pressure educational research grants program. The investigators we support with this mechanism are trying to define which educational approaches are most effective in helping hypertensive patients maintain their therapy. In this regard we view hypertension as one example of a chronic disease problem in which the Institute helps provide an understanding of the broad behavioral science principles which effect health seeking behavior. We are asking the question what can we do to help people change their lifestyle in a way that is in reality and also is seen by the individual as contributing to improved quality of life as well as longevity.

We support research grants in this area that are testing many different techniques: physicians signing contracts with patients to follow through on a regimen; the use of pairing patients to look after each other, et cetera.

Perhaps the most important thing we have done has been to sponsor two large workshops: one, a national heart and lung working conference on health behavior to which we invited many of the leaders in the behavioral and psychological and sociological communities to review the behavioral problems associated with heart, blood, and lung diseases and make specific recommendations as to procedures that might currently be applied and needed research. Second, a nutrition-behavior conference brought together investigators from our Lipid Research Clinics, the multiple risk factor intervention trial, specialized centers of research program, and the National Cardiovascular Research and Demonstration Center to share the interim results of their studies. Some 100 members representing three related specialties—medicine, behavioral science, and nutrition—were brought together to explore how best to use the expertise of the behavioral scientists to augment the skills of the practicing nutritionists and physicians in efforts to change health-related dietary patterns within the U.S. population. Both workshops emphasized behavioral science opportunities in chronic disease control.

Mr. FLOOD. You are still stressing the term medication?

Dr. LEVY. We talk about adherence, compliance to both diet and drug programs, and at the same time, Mr. Chairman, we are looking with these same groups at new nondrug therapies.

We are looking at what are the facts or fallacies about the effectiveness of, for example, transcendental meditation or bio feedback.

Because no drug therapy is totally without risk, we are certainly eager to pursue effective alternative therapies. Our first step, which we expect to complete soon, is to assess as accurately and objectively as possible, the current state-of-the-art of these alternatives so we can support the most productive research to hasten the appropriate application of nondrug therapies.

HYPERTENSIVE DRUGS

Mr. FLOOD. Let's come back to earth for a minute. The problem is unless we improve the drugs that are used in treating hypertension, then all our efforts—all these great efforts you are making about screening and treatment—are going to fall pretty short of their goal, aren't they?

Dr. LEVY. Yes, Mr. Chairman, it is really a two-pronged attack. One is designed to help us help the physician and help the patient following through on existing medication which can lower the blood pressure but have side effects. Another major venture and goal, and a major ongoing effort of our high blood pressure specialized centers of research, is to try to find treatments that are more effective. We have some very exciting leads in terms of using drugs based on the normal physiologic mechanisms by which blood pressure is controlled. These new drugs either prevent the release or block the activity of hormones which can raise blood pressure. These are specific biologic inhibitors of these naturally occurring hormones. These agents are now being tested in experimental animals and in man. They dramatically lower blood pressure and leave apparently fewer side effects. But this approach is still in the experimental stage. We must continue to develop more effective drugs without side effects.

PEDIATRIC PULMONARY DISEASE

Mr. FLOOD. Another one of your research activities is in the field of the pediatric pulmonary disease. You, of course, are well aware that the maternal and child health program has 10 of these centers. Do you work with these centers and do you provide any financial support of any kind?

Dr. LEVY. I am pleased to say that we communicate and are now trying to integrate our efforts with both the pediatric pulmonary centers and the administrative arm who run or administer the program in HSA, the Bureau of Maternal and Child Health. What we have looked at and realize is that these centers contain large resource pools of children with problems. What we have in our specialized centers of research in pediatric disease is reseach expertise. Putting these two groups together, establishing a working dialog between the maternal and child health service program, Health Services Administration, and the National Heart and Lung Institute, is essential.

Mr. FLOOD. Do you do that?

Dr. LEVY. This is what we have begun to do since September.

Mr. FLOOD. Do you give them any financial help?

Dr. LEVY. We have not given them any financial help up to this point, Mr. Chairman, but there has been talk about doing some of the clinical research investigations at the pediatric pulmonary centers.

There are several cities within the United States where both maternal and child health services pediatric centers and national heart and lung institute pulmonary specialized centers of research exist. Recognizing the different orientation of research but noting the complementary nature of project activities and opportunities, our two agencies have established working interrelationships and information links.

SUDDEN INFANT DEATH SYNDROME

Mr. FLOOD. Are you doing any kind of research at all that is going to lead to the solving of the problem of this sudden infant death syndrome?

Dr. LEVY. Yes; Mr. Chairman, you know, the Child Health Institute supports a large program in this area.

Mr. FLOOD. Yes.

Dr. LEVY. We support two programs that we think may give some lead. It is very likely that sudden infant death syndrome is due to a multitude of things. We have developed some leads from our intramural program that the inheritance of an abnormal conduction system in the heart may predispose children to sudden cardiac death. We see this in adults, and have seen it by history in children.

Mr. FLOOD. Speaking of the pediatric pulmonary defects? Are you identifying with that?

Dr. LEVY. It does appear that the respiratory system and its control is different in some children, especially sometimes modified by mild intercurrent infection. This is being looked at in the pediatric pulmonary specialized centers of research.

PULMONARY NATIONAL RESEARCH AND DEMONSTRATION CENTER

Mr. FLOOD. One of the projects also that you support is a national research and demonstration center in the pulmonary diseases.

By the way, where is it located?

Dr. LEVY. That is in Vermont, at the university in Burlington, and it is a center that runs the gamut from basic research to education.

Mr. FLOOD. How much do you put in that center?

Dr. LEVY. That budget is about $1¼ million per year.

Mr. FLOOD. We understand that center is looking at the occupational pulmonary diseases resulting from exposures to dust and fumes, et cetera. We have had a lot to do with that with other programs such as the National Institute for Occupational Safety and Health. That is why we are concerned about it. Do you have any specific examples of the kind of work that center is doing?

Dr. LEVY. The establishment of a research and demonstration center at the University of Vermont College of Medicine will tie together and intensify efforts and resources toward the control of respiratory disease in Vermont, a State with one of the highest respiratory ailment rates in the country. The primary function of this center is to close the gap between new medical knowledge and its dissemination and application. The center is doing some basic work trying to understand the mechanism of the disease that occurs. Perhaps most exciting is the work that that center is doing in terms of making the community—and this is all of Vermont—aware of the problems in chronic fibrotic lung disease, pneumoconiosis. They have set up systems for early detection, systems for self-instruction, educational systems for outlying medical facilities, so they can recognize this.

The Vermont center has organized a collaborative effort between the medical school and the Vermont State Department of Health. The object is to make a significant impact on the reduction of morbidity and mortality due to occupational exposure to toxic substances. The first phase is to establish significant correlations between respiratory dis-

orders and levels of exposure to toxic substances in workers in quarries and farms, et cetera. In the second phase, investigators will develop standards for occupational exposure which will be utilized by participating industries.

Mr. FLOOD. This isn't a parochial operation for Vermont, is it?

Dr. LEVY. No; this is the demonstration aspect of a research center.

Mr. FLOOD. How do you coordinate the work of this center that you are talking about now with the activities of the National Institute of Occupational Safety and Health that we spent so much time on? This worker is a taxpayer too, so he is concerned both ways here.

Dr. LEVY. The integration and coordination is done primarily at the personal level. Our Director of the Division of Lung Disease has a constant dialog with his counterpart in the Institute of Occupational Safety and Health. They have served on the review board for our programs so they know what we are doing and can tell us what they are doing, and this is as effective a dialog as we can accomplish right now.

Mr. Chairman, if I may digress for a moment. I gave you a figure for the pulmonary research and demonstration center, and I said it's somewhat more than $1 million. It is at that figure, because the center at Vermont is unique. The research portion of that is funded by a specialized center of research, so that, added on to the research and demonstration center, would be the value of the specialized center of research which is now undergoing competitive renewal and is about $500,000.

EDUCATION PROGRAMS

Mr. FLOOD. Now, let's speak again about education programs. What kind of education programs are you supporting for medical personnel, all kinds of medical personnel—the ones who are making the first contact with the patient who has a heart attack or any kind of acute respiratory insufficiency of any kind at all? What I have in mind now is the emergency room physician, or the emergency medical technician, the ambulance attendent.

What are you doing about that in your educational program?

Dr. LEVY. Mr. Chairman, let me give you some examples because if I talked about what we were all doing we would be here for a long time.

In terms of the emergency room, we can talk about the fact that in our sickle cell comprehensive centers we have developed a set of guidelines as to what the emergency care physician should think about, what might the patient be suffering when he comes in with sickle cell disease, in pain, what should be ruled out, how should it be treated.

This has effectively eliminated a tremendous backlog in terms of the problems that many of these patients had when they came in.

Mr. FLOOD. I am talking about what kind of education programs you are conducting with the medical personnel.

Dr. LEVY. We also have a program for medical personnel in emergency rooms in the pulmonary area. This program is designed to develop more effective ways to teach emergency medical services personnel how to deal with respiratory distress.

Two educational programs are being developed for early treatment of acute respiratory insufficiency in adults to reduce the morbidity

and mortality resulting from this disease. The first program is aimed at professionals with no special training in respiratory disease. The second is for nonprofessional personnel likely to have first contact with patients suffering from acute respiratory insufficiency. Both innovative and well-established educational methodologies are being employed. Three approaches to information dissemination are being tested concurrently in order to assess their relative effectiveness.

At present, the most common cause of death in the newborn is respiratory failure. It may be prevented if respiratory insufficiency can be anticipated or recognized at onset and therapeutic measures instituted promptly. To identify those infants at risk requires recognition of prenatal conditions in the mother and perinatal conditions in the infant which may lead to respiratory problems in the neonate. Prematurity, which is frequently associated with neonatal respiratory distress syndrome, that is, with hyaline membrane disease, must also be recognized and treated without delay if a maximum number of infants are to be saved.

The educational programs being developed are directed to physicians, nurses, physicians' assistants, midwives, and other professionals involved in prenatal care, delivery, and neonatal care. These individuals are being taught to recognize respiratory distress and initiate early treatment. The educational programs are for use in those geographic areas and community settings lacking intensive care facilities for neonates.

Mr. FLOOD. What about ambulance attendants?

Dr. LEVY. In the Houston Research and Demonstration Center we are participating in instructing many individuals in what is called cardiopulmonary resuscitation. This is a technique that can be life saving if the person is reached in time in terms of reviving the patient and starting his heart beating again.

We support these programs in part through our Research and Demonstration Center in Houston. We also support this through our research program on sudden cardiac death. This program was established in 1970. It has supported many of the programs which have become the keystones in the emergency medical services system—for example, the Seattle heart watch program and the cardiopulmonary part of the emergency rescue system in Miami. Indeed, the developments in therapy which came out of these programs are now being widely instituted throughout the country. The research effort is now pushing one step earlier; namely, to undertake research at the underlying mechanisms of rhythm disturbances which cause cardiac collapse and to develop preventive therapy. Death from sudden cardiovascular collapse is preventable much more often than we realize. We also look forward to therapy which will reduce the frequency of sudden cardiovascular collapse. However, throughout all of this we are very insistent on making sure that the fruits of this research are actively applied to patient care.

EMERGENCY MEDICAL SERVICES

Mr. FLOOD. Are all these training programs coordinated with the emergency medical service, that is the program in the Health Services Administration.

Dr. LEVY. We support it.

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Mr. FLOOD. Are they coordinated?

Dr. LEVY. They are coordinated, and there is an emergency medical service coordinating committee.

Mr. FLOOD. How?

Dr. LEVY. Through a coordinating committee my associate director for cardiology programs as the NIH representative to this coordinating committee.

Our primary contribution to the emergency medical services system has been the development of much of the fundamental and applied information on therapeutic techniques. Our current effort is focused especially upon basic research on the mechanisms of heart rhythm disturbances and upon their prevention, as well as identification of persons who are at high risk for sudden cardiac death.

Mr. Chairman, there are many other education programs we would mention ranging from our efforts in hypertension to the development of new material on blood component therapy. In all of our efforts we are dedicated to finding better approaches, in short doing research so that others, better equipped than ourselves, may more effectively educate the general public and the professional community.

HEMOPHILIA

Mr. FLOOD. Now, in some of the material you gave us here, you state that a treatment of hemophilia A has been revolutionized by a new procedure. Can you in layman's terms explain what that new procedure is, and of ocurse, what it means in terms of clinical management of hemophilia?

Dr. LEVY. The problem with the hemophiliac is he is missing an essential clotting factor—so called antihemophilic factor—and bleeds readily whenever he bruises or cuts himself.

In the old days the way to protect a patient was first to give him a unit of normal fresh whole blood that would have the factor in it and could stop the bleeding.

Ten years ago it was found that by allowing plasma to quickly freeze, and then thaw at 4 degrees centigrade, a precipitate, now called cryoprecipitate, is found which contains a high concentration of this antihemophilic factor. This concentrated material can be infused in the home by the patient himself at the first signs of bleeding problems. Furthermore, from this, or from fresh frozen plasma, a true concentrate can now be produced by fractionation techniques. This concentrate, so-called by antihemophilic factor concentrate, can be dispensed in a stable, powdered form which does not require refrigeration.

Mr. FLOOD. What does that mean in the terms of clinical management of hemophilia?

Dr. LEVY. In terms of the patient we can now give the patient a known quantity of antihemophilic concentrate when he injures himself, bruises himself, and can raise his level of antihemophilic factor to normal, and, therefore, prevent the occurrence. By providing concentrates of antihemophilic factor that can be carried with the patient wherever he goes, we have made him more mobile and provided him an essentially normal lifestyle. Furthermore, we can give such materials prophylactically prior to surgery or dental work, so that, now,

even heart or brain surgery can be performed on the hemophiliac without serious abnormal bleeding.

What we don't know, Mr. Chairman, and we may find out at some point down the road is whether prophylactic administration of antihemophilic factors and concentrates will totally eliminate the crippling bleeding into the joints and makes the lives of these patients perfectly normal.

Mr. FLOOD. This committee appropriates $3 million for initial implementation of hemophilia treatment—the blood separation program. We were told there is a shortage of the appropriate blood products required for the hemophiliac. Well, will this procedure you are talking about help to alleviate that problem?

Dr. LEVY. The preparation and distribution of antihemophilic factor concentrates in adequate amounts, at a reasonable price, will have that effect. The development of these products is now, unfortunately, tied to the preparation of other major components of whole blood, such as red cells, platelets, and albumin. One can perform what we call plasmapheresis, which doesn't require the patient to give up his red blood cells. Using plasma so obtained, and the use of so-called salvage plasma from whole blood donations from which red cells or other components have been separated for transfusion, one can increase the supply of materials for preparation of antihemophilic factors. What this procedure would do would be to make both antihemophilic factors and other blood products, which are often in short supply, available to the community.

Mr. FLOOD. All right; we understand there are 67 centers all across the country that provide some degree of hemophilia care. What effort are you making to familiarize these centers with this new treatment procedure?

Dr. LEVY. Any physician treating hemophiliacs, whether or not as part of a so-called center, is familiar with, and has available to him, these products. Furthermore, we have over the last year gotten together most of the groups who are involved in hemophilia care, the patient, the user, the blood banks. We have held two large meetings discussing the methods. The problem, Mr. Chairman, is that, if all of the blood donations went into making this antihemophilic concentrate, then one might lose blood products that are needed for other people. If we made this concentrate available for widespread prophylactic use—constant daily infusion—for all of the 25,000 or so hemophiliacs in the country, it has been calculated that all of the available blood supply in the United States and then some could be used for this one purpose alone.

SICKLE CELL DISEASE

Mr. FLOOD. You have touched on this a few minutes ago, but how close is your Institute to developing a therapy for the sickle cell disease?

Dr. LEVY. As you may know, Mr. Chairman, we thought we were very close a few years ago.

Mr. FLOOD. I know that.

Dr. LEVY. Those forms of therapy have not worked out. Right now I would say that we are exploring several leads, including the attempt to use the agents that were promising before, cynanide and

urea, extracorporeally, really outside of the body, to try to affect the red cell proteins without affecting the other blood proteins.

Mr. FLOOD. How close are you to developing a new therapy?

Dr. LEVY. I would say our therapy right now is palliative, ameliorating.

Mr. FLOOD. At what dollar level are you operating at now?

Dr. LEVY. In 1976 about $18 million was spent for the total sickle cell disease program, including screening and counseling and in 1977 the total may drop to a little bit below $17 million.

I might say, Mr. Chairman, that we are evaluating a new lead this year in basic research. It has been demonstrated that the infant with sickle cell disease is protected for the first 6 months of his life by another hemoglobin, we call it fetal hemoglobin which circulates for about that time.

Protection does increase in some disease states. If we can figure out how to control it or reverse it we can hopefully apply this to the protection of the patient with sickle cell disease. After birth the so-called adult hemoglobins are produced, normal in the case of normal patients and so-called sickle hemoglobin in patients with sickle cell anemia. It is the rigidity and insolubility of this sickle hemoglobin that makes the red corpuscles in sickle cell anemia abnormal, easily destroyed, and tangled up in the circulation. If we could find a way to make the blood producing cells revert to the production of the more soluble fetal hemoglobin normally produced in utero, instead of the sickle hemoglobin produced in adults, the red corpuscles of these patients might behave more normally, and the disease might be ameliorated, if not cured. This research involves very basic mechanisms of gene action, and while somewhat of a gamble, is theoretically very promising.

Mr. FLOOD. How much again in 1977?

Dr. LEVY. Mr. Chairman, I commented that there will be a reduction of about $1.2 million in the program in 1977.

COOLEY'S ANEMIA

Mr. FLOOD. Now, the other genetic disease that we get a great deal of pressure about, I know you do, and we do, is Cooley's anemia, so will you describe research efforts in that area?

Dr. LEVY. Cooley's anemia is a disorder which involves the inadequate production of one of the parts of the hemoglobin molecule so these patients have very severe anemia, requiring transfusions from early life on. Our research involves study of the basic mechanism the gene, the message that is carried by the messenger RNA, and that creates hemoglobin, the thought being perhaps someday we can put the messenger back or increase its activity. We are also doing clinical research in this area and we do have some promising signs of therapy.

The problem with the Cooley's anemia patient, after multiple transfusions for anemia, is the decomposition of iron all over the body. It interferes with the function of the heart and other body organs. There is an agent called desferrioxamine or Desferal, which is capable of binding iron.

We have done studies in the NIH Clinical Center that shows constant infusion of Desferal is capable of removing large amounts of iron from the body organs of patients with thalassemia, or Cooley's anemia.

We are excited enough about the effort that this year we have just released a request for applications to get outside investigators to look at the cardiac function, endocrine function after using Desferal to hopefully demonstrate not only that we are removing iron, but we are making these patients' hearts healthier, these patients are being given added time in life.

NATIONAL BLOOD POLICY

Mr. FLOOD. In your material you state that you have entrusted implementation of a national blood policy to the American Blood Commission. How are they progressing? Are they having any specific problems?

Dr. LEVY. The American Blood Commission [ABC] was formed in April of 1975 for the specific purpose of implementing the national blood policy through the private sector. The ABC accordingly, is a voluntary organization made up of blood banks including the American National Red Cross, the American Association of Blood Banks, and the Council of Community Blood Banks as well as other organizations such as the American Hospital Association, the American Medical Association, the National Hemophilia Foundation, the Leukemia Society of America, labor unions, and other representatives of the public. The first task was to bring together these various groups, many of whom have not collaborated with one another in the past. The stated aim of the ABC, to which the NHLI is fully committed, is to bring into being a safe and adequate supply of blood and blood products for all Americans.

The ABC created a series of task forces dealing specifically with: (1) the regionalization of the blood supply on a nationwide basis; (2) the creation of a national data bank to provide information about needs and demands in the blood field; (3) the establishment of a common procedure for identifying, labeling, and processing of blood; and (4) the problems in the area of blood donor motivation and recruitment. The NHLI has contracts with the first three of these task forces and intends to support the fourth task force, that on donor motivation and recruitment, when a properly designed study plan is submitted. We are also collaborating with the Bureau of Biologics in establishing an initial although more limited data base, the blood establishment, inspection, and registration system [BEIRS], which will provide information about the operation and staffing of the now existing blood banks to tide us over the interim period until a true national data base in the blood resources field becomes available. An underlying philosophy of the ABC to which we subscribe is the creation of an all-volunteer donor system throughout the country in order to minimize the increased hepatitis risk known to be associated with a large segment of paid donor population.

Mr. FLOOD. I said if you had any specific problems and I guess you are listing them.

Dr. LEVY. That is exactly right.

DIABETES RESEARCH

Mr. FLOOD. By the way, I hope you know this, that in our report on the 1976 appropriation bill, the committee report, we directed, capital D, the Heart Institute to use a portion of that increase in funds to support diabetes research. Have your carried out the directive?

Dr. LEVY. I am pleased to say, Mr. Chairman, that on March 1, a request for applications for investigators to study the cardiovascular aspects of diabetes will be released to the scientific community.

Mr. FLOOD. How much do you intend to spend in this research in 1977?

Dr. LEVY. Well, we hope, Mr. Chairman, now that we have the funds for 1976, to increase our expenditure for diabetes from some $5½ million to $7 million or more in 1976. In 1977 that will officially, along with everything else, have to be reduced.

Mr. FLOOD. What kind of activities?

Dr. LEVY. Well, we have many different kinds of activities in diabetes. The specific new action is to try to understand better the etiology, pathophysiology mechanisms, and treatments of why 80 percent of the diabetes patients die of cardiovascular disease and why sudden death is so common;

What is there about the heart muscle itself that predisposes these patients to heart failure? Why do the patients develop gangrene of the lower limbs five times more frequently than the general population? All of these aspects will be looked at.

Our continuing ongoing research deals with the effects diabetes has on the micro- and macro-circulation and deals with epidemiology. It was our studies in Framingham and Tecumseh that first pinpointed the fact that diabetes was a clear, undeniable independent risk factor in heart attack and stroke.

Mr. FLOOD. Now you know a directive when you see it.

Dr. LEVY. Yes, and we have responded to it.

EMPLOYMENT POSITIONS

Mr. FLOOD. How many of the 747 positions authorized for your Institute have actually been allocated?

Dr. LEVY. Mr. Chairman, we are still at the present time operating under a ceiling.

Mr. FLOOD. How much has been allocated?

Dr. LEVY. None. We have at the present existing ceiling, which is 683. We are told that the allocation will come to us soon.

Mr. FLOOD. How many unfilled jobs do you have at the present time?

Dr. LEVY. At the present time and over the past few years all of the positions that we have been allowed have been full when we could fill them.

The problem has been our budgeted ceiling, Mr. Chairman. The budgeted positions and those which we are allowed to fill under our "ceiling" do not necessarily coincide.

Mr. FLOOD. Mr. Early?

HEART DISEASE MORTALITY

Mr. EARLY. Thank you, Mr. Chairman.

Doctor, I find your statement interesting and the statistics revealing, but I was on a platform in 1955 with Dr. Paul Dudley White in Massachusetts and he told the audience, at that time, that within 1 year, that is by 1957, the medical profession would have mastered the heart, that within 1 year there would be no fatalities because of failure of the heart, and then I see in your opening remarks, half of all deaths in the United States can be attributed to cardiovascular diseases.

Dr. LEVY. Mr. Chairman, Dr. White was on our advisory committee on two occasions. He is considered by many the father of modern clinical cardiology. Dr. White perhaps sometimes was being prophetic, sometimes being hopeful.

We have made tremendous advances. Let me say that I have talked about ischemic heart disease, but in terms of death rates from all cardiovascular causes our advances are striking. The death rate for cardiovascular disease 25 years ago was 404 for 100,000 subjects per year. It has now been reduced to 333, a reduction of 25 percent in this major killer problem.

I wish I could say we would do it overnight. I am excited, I am pleased that we are making the turn, that we are doing something.

DIAGNOSTIC COSTS

Mr. EARLY. You spoke in the opening remarks of a heart monitoring device the patient could use at home. How much would that device cost?

Dr. LEVY. Right now and and probably for a long time it will be an experimental device. The device to which I was referring is a small amplifier and tape recorder for recording the electrocardiogram. Such apparatus currently costs about $1,500. The patient wears the apparatus over his shoulder or on his belt as he goes about his activities. The tape recordings then have to be analyzed with some fairly sophisticated equipment. A typical 24-hour monitoring costs something on the order of $100.

Mr. EARLY. On page 3 of your statement, what is the average cost to the patient of this computer-based X-ray image technique mentioned?

Dr. LEVY. The cost of medical procedures varies. In part, this is determined by the exact nature of the procedure as well as other matters. I think these computer-assisted X-ray image techniques cost on the order of $50 to $100. However, we are also very excited about ultrasonic techniques.

Mr. EARLY. What is the cost?

Dr. LEVY. The apparatus for ultrasonic analysis is very much less than for X-ray. For the simplest ultrasonic apparatus, that used for detecting pulsatile blood flow in the extremities, the cost is a few hundred dollars. For the much more sophisticated apparatus used in actually examining the heart and "looking at" its anatomy, the apparatus is on the order of $10,000 or $15,000.

The cost of such an examination again varies. A major cost is the physician's time, since this is something he must do himself. However, the very important cost saving is when it is compared to the X-ray technique. In the first place, with the ultrasonic methods it is possible to examine the heart and to characterize its internal structures, for example, its valves and their movement, the thickness of the heart muscle, et cetera, without hospitalizing the patient and, most importantly, without having to inject anything into him. In other words, the patient does not have to undergo a cardiac catheterization. He simply is examined with a hand-held probe which both emits and detects the ultrasonic signal. Thus the associated costs are also tremendously reduced.

These techniques are moving rapidly from the research setting into practical clinical use.

DISSEMINATION OF RESEARCH FINDINGS

Mr. EARLY. Describe the process by which hospitals and clinics are informed of the new research findings that are taking place at your Institute?

Dr. LEVY. We have several different systems for dissemination of information. We use our research and demonstration centers as resources to get information into the community. We help develop and sponsor instructional classes and prepare educational materials.

We have a direct mailing system to hospitals and to the groups the Chairman and I spent time with yesterday, the American College of Cardiology, and the American Heart Association. All have very active continuing medical education programs.

We interrelate and integrate with them and we have our own activities in continuing medical education, as we talked about before in high blood pressure.

Mr. EARLY. Therefore, this committee could feel confident that this information is being disseminated to the hosptials?

Dr. LEVY. We are spending some $12 million to $13 million a year right now in dissemination. I would like to say I feel confident it is getting out to everyone. I can't say that.

Certainly we could do more and we could do it more expeditiously.

COSTS RELATED TO HEART DISEASE

Mr. EARLY. Can the hospitals afford to purchase the new equipment and facilities and if so, is this supply unlimited?

Dr. LEVY. The echo equipment is not expensive in comparison to what other apparatus would cost which would do a comparable job. The much more elaborate X-ray apparatus is being installed fairly widely, but of necessity it is being restricted more to the larger centers.

Mr. EARLY. Well, if this equipment is inexpensive, why don't I see medical costs going down?

Dr. LEVY. Mr. Early, let me say when one looks at cardiovascular disease, you know, it is estimated I think I said in my opening statement, that is costs $40 billion a year. When one looks at the $40 billion, $22 billion, more than half of it is not for hospital costs. That cost is for the loss of life prematurely. If one wants to talk about hospital care costs, and cardiovascular disease going down, let me point out that in the last two decades the length of time for a patient to be in the hos-

pital with a heart attack, and you know the dollars that are spent each day for a patient in the hospital, the length of time has fallen from somewhere well over 21 days, so that today, the national average is 17 days, and in an uncomplicated heart attack patient it can be less than 10 days. There is a tremendous saving in cost.

Mr. EARLY. Would you supply the committee with a breakdown of why it is fiscally unsound to make these cutbacks in this area, and where it is going to cost us more money in the long run? It is awfully discouraging.

[The information follows:]

COST BENEFITS

It is difficult to make precise estimates, but it is not an exaggeration to state that 1 day in the hospital for a patient recovering from a heart attack easily costs $200. With a half million patients hospitalized annually with a heart attack, a 1-day saving in the average hospitalization would represent a $100 million reduction in the annual hospitalization cost. This is only a grossly approximation, but it illustrates the major impact of even very moderate reductions in costs. However, I would like to emphasize that it is not just a matter of dollar savings. It is also a matter that people who get out of the hospital earlier—because they are well enough to—recuperate more quickly, return to active work sooner, are more enthusiastic about their outlook, and end up better rehabilitated. But clearly on the sheer cost-effective basis, medical research does pay off.

A specific cost-benefit analysis has been made in the area of hypertension: "A Cost Benefit Analysis of Model Hypertension Control" by John Stokes, III, M.D. and Duncan C. Carmichael. This was published in May 1975, by the NIH's national high blood pressure education program, a copy of which is transmitted to the committee. A summarization of this report follows:

THE COST/BENEFIT OF HYPERTENSION THERAPY—A SUMMARY

The concept of spending money to save money is bruited about often. It is less often supported by substantive analysis. In the case of hypertension therapy, which does have a cost that endures for the lifetime of the patient, a cost/benefit estimate by the National Heart and Lung Institute suggests that a considerable investment can be made by society which produces, in effect, a profit. Using a very conservative approach, our analysis suggest that for every dollar society invests in hypertension therapy, it receives a return of $1.24.

The details are present in "A Cost-Benefit Analysis of Model Hypertension Control," available from the National Heart and Lung Institute. In summary, an equation is set up with direct medical costs of hypertension therapy on the one side and avoided medical costs of hypertension's complications, as well as avoided loss of income on the other. Factors considered included numbers of patients at various blood pressures; alternative tests and therapies in common usage, and their costs: effectiveness of therapy in persons with various blood pressures; the incidence of complications in treated versus untreated patients; the extent of lost income due to incapacitating complications or hospitalization and the value of present versus future earnings. The table below presents the outcomes of these calculated factors.

BENEFIT-COST RATIOS FOR HYPERTENSION CONTROL

Group	Total benefit to cost	Earnings' benefit to cost	Medical benefits to cost
Male:			
35 to 44	2.12	1.90	0.22
45 to 54	1.89	1.57	.32
55 to 64	1.19	.78	.40
Female:			
35 to 44	[1].75(1.14)	.63(1.02)	.12
45 to 54	.57 (.78)	.36 (.58)	.20
55 to 64	.39 (.45)	.10 (.16)	.29
All groups	1.24(1.35)	1.00(1.11)	.25

[1] Values in parentheses indicate the benefit-cost ratio under the assumption that female earnings are equal to male earnings.

The overall benefit-to-cost ratio is 1.24 to 1, indicating that treatment returns 25 percent more than it costs. In terms of the ratio of each of the two benefit components to cost, additional earnings account for about four times the benefit that reduction in direct medical expenditures account for.

The variations of the benefit-cost ratio and its component ratios with age and sex are also interesting. Overall, the ratio decreases with age, however, the partial ratio of direct medical cost benefits to total cost increases with age. For women the benefit-cost ratio is significantly lower than for men—since part of this difference is due entirely to the fact that women earn less than men, we have also estimated the ratio values under the assumption of equal earnings, and these values appear in parentheses in the applicable parts of the table. Even with the assumption of equal earnings, women still show a lower ratio than men.

Expanded treatment—What effects on the benefit-cost ratio would there be if large numbers of previously untreated hypertensives request treatment? According to our assumptions, 8.498 million persons between 35 and 64 years of age would enter treatment. Of these 2.807 million—15 percent—would be in nondrug therapy, and 5.691 million—85 percent—in drug therapy.

As physicians' services are by far the scarcest resource in medical treatment, we will first consider the increased demand generated here. In 1972, there were approximately 1 billion physician visits outside of hospitals, an average of about 5.5 visits per person. If treatment were to cover the entire hypertensive population, we would estimate a gross increase in the long run of about 34 million annual visits or 3.5 percent in total physician visits. In terms of dollars, on an approximately annual basis there would be an increased demand for physicians' services of about $340 million, or about 2.5 percent of the total paid for such services in 1970.

The incremental demand for physicians' services in the first year of an individual's treatment would be twice as great, according to our treatment assumptions. If, over the course of 5 years, all persons needing treatment would seek it, then the gross incremental demand for services in this period would be approximately 3 percent higher than at present. On the other hand, as a hypertensive patient is controlled, there is a decremental effect on the demand for physicians' services for the care of cardiovascular disease and kidney disease, of approximately one-quarter of the gross increase estimated. There is another potential decremental effect as well, caused by our overlapping with present services. We have not, however, estimated this effect, preferring instead the more conservative method of allocating the cost of any shared service to hypertensive care. We assume, therefore, that the net decrement would be 25 percent and the net increase in demand and for physicians' services even during a 5-year buildup period would be only 2.3 percent.

Mr. EARLY. The chairman has to go to the floor every year like he is a big spender and you are telling us we can spend money to save money.

Dr. LEVY. I would agree with the concept that in our view spending money now in this research, in the clinical advances will result in less expenditure, and would save more money.

HYPERTENSION BUDGET

Mr. EARLY. I should think that you could make a good fiscal case to present to the chairman, and that he could decide whether or not to put it in the record on high blood pressure. Your reply to the chairman was that you propose to reduce the national high blood reserve education program $400,000, and it is only a $3 million program. That is a 20-percent cut.

Dr. LEVY. I would be delighted to provide that information. In fact, we will take a try at it. But we have a paper about this thing, half an inch, which is a cost benefit study in the treatment of high blood pressure, and we have circulated this and what it shows is that one gets back $1.25 for every dollar one puts into high blood pressure treatment, in terms of savings, morbidity, and mortality.

Mr. EARLY. Therefore, the administration is going in the wrong diretion to suggest a 20-percent cut, where we are getting $1.25 for every dollar.

You know, I really feel, I feel it out in my district, that people are becoming better educated on the subject of high blood pressure, and I think the TV has been very effective, the ads and everything else. But now, is this reduction going to call for a termination or reduction in that campaign? Your statistics only show you have made inroads. You started at 12 or 15 percent and you are now up over 40 percent penetration. You are going in the right direction, but that still leaves 60 percent of the population that you are not getting to.

Dr. LEVY. We are resource limited now. We are not idea or opportunity limited.

Mr. EARLY. I would think there would be a hue and cry from the medical profession in opposition to these cutbacks.

Dr. LEVY. I think from time to time in the past the chairman has heard that.

Mr. EARLY. Until the chairman put the pressure on to get the medical profession to say we should override, I don't remember seeing any letters from medical professionals on the subject. And I would think the pressure should come from the profession.

TRAINING

Mr. EARLY. Let me ask this: The techniques which you mention on page 3, which you say are inexpensive—if these techniques were put into effect now, would you have the personnel capable of operating them?

Dr. LEVY. I am delighted you asked that question. The engineering and instrumentation techniques utilized in the development of the echo, ultrasonic, an d X-ray apparatus represents biomedical engineering research. The early clinical investigation of these devices was performed by expert clinical researchers. The actual widespread use of the device, by medical practitioners throughout the country, depends upon their training. If provision is not made for training physicians in these techniques—the practicing physicians and physicians coming out of our medical schools—then we must either take those who have dedicated a lifetime to research and move them into the practice area, in which they may not be making their greatest contribution, or be left with advances which are not applied to patient care. We simply cannot let this happen.

Mr. EARLY. Will there be money for training the manpower?

Dr. LEVY. There is no money for new training in our fiscal 1977 budget. In fact, that budget assumes any training we began in 1976 was for 1 year, and that we did not have any new training.

Dr. FREDERICKSON. You will be training under fellowships, under this budget?

Dr. LEVY. No, we will be continuing a certain number of fellowships approved before, but there is no money in the present budget for new training starts.

HIGH BLOOD PRESSURE PROGRAM

Mr. EARLY. So we will have the machines but we won't have the people to operate them. The $600,000 cut in the blood pressure program, where will that cut be, in the educational end?

Dr. LEVY. I would hope we could act as effectively as possible to minimize the effects of the cuts on the community, what the program has done, and the program's momentum. I would hesitate to speculate what we would have to cut. I would like to speculate that we might not have to cut, but right now what we have done, having just received a budget for this year and just looked at a budget for next year, has been to in part indiscriminately apply this reduction of $28 million across all of our programs.

We are very pleased and proud of the high blood pressure education program. We would hope we would continue it with the momentum it has. The problem has to do with competing excellent priorities and needs.

Mr. EARLY. Or making a case whereby we would save money in restoring that $28 million.

Thank you, Mr. Chairman.

CARDIOVASCULAR DEATH RATE

Mr. MICHEL. You mention in your statement that cardiovascular diseases account for over half of all deaths in the United States. What does that amount to in numerical terms?

Dr. LEVY. Major cardiovascular disease continues to be the No. 1 killer in the United States. They have a devastating effect on the health of our citizens and on the Nation's economy. More than 30 million Americans suffer from these diseases. According to provisional data from the National Center for Health Statistics, there were 1,933,000 deaths in 1974. Of these the major cardiovascular diseases caused 1,017,350 or 52.6 percent.

Mr. MICHEL. Is this figure continually rising, or is it on the decline?

Dr. LEVY. For about a quarter of a century deaths from heart disease increased steadily. Then, as I indicated in my prepared statement deaths from coronary heart disease declined by 10 percent from 1968 to 1973. There are indications from 1974 data that this decline is continuing.

IRREGULAR HEART RHYTHM

Mr. MICHEL. You mention a finding that the overwhelming majority of sudden cardiac deaths occur because of an irregularity in heart rhythm. And that you know how to correct this. What percentage of potential deaths would you estimate are now prevented because of this knowledge?

Dr. LEVY. One has to make an estimate on this, but a substantial majority of out-of-hospital deaths and even a good number of inhospital deaths from coronary heart disease are due to rhythm disturbances. On this basis, I am sure that there are in excess of 300,000 deaths from rhythm disturbances. Inside the hospital, we are now quite good at preventing rhythm disturbance deaths. This has been a major cause of the reduction of inhospital mortality from about 30 percent to below about 20 percent over the past decade. However, many of the drugs we use in the hospital have to be given intramuscularly or intravenously, techniques which do not lend themselves to chronic use outside the hospital setting. Further, the risk of dropping dead suddenly

is not nearly as high in the ambulatory population as in those who are hospitalized with a heart attack.

There have been some very promising preliminary clinical trials with antiarrhythmic agents. If we can believe these—and while they are tantalizing, we are not at that point where we can accept these as recommended therapy—chronic therapy might be expected to reduce mortality of those surviving a heart attack by one-third in the first year. I suspect that because of our use of antiarrhythmic agents now we are probably saving several thousand lives each year. I can project and estimate—perhaps speculate is a better word—that if these techniques are found effective, reliable, and safe we could hope that on the order of 50,000 lives might be saved annually.

IRREGULAR HEART RHYTHM

Mr. MICHEL. How long do you think it will be before we are able to prevent the irregular rhythm before an attack occurs?

Dr. LEVY. We are studying the feasibility of a clinical trial to test such antiarrhythmic regimen. If this is deemed feasible, I envison it would take 3 years to undertake this study and have substantial results back. At that time, we would be in a good position to make a substantial impact upon the control of lethal arrhythmias before a heart attack occurs.

NONINVASIVE INSTRUMENTATION

Mr. MICHEL. You mention some techniques such as ultrasound and X-ray image intensification which allow the early detection of cardiac disease, often long before clinical signs develop. These are apparently being used presently on a selective basis. What is the potential here, and how long before we can expect widespread use?

Dr. LEVY. The ultrasound and echo-image intensification techniques are being used selectively at this time because their applicability is considerable but far from universal. For example, the leading type of heart disease is that of coronary heart disease. By our present techniques, we cannot recognize coronary heart disease, either by ultrasonic methods or by X-ray techniques until after a heart attack has occurred, or until a significant impairment of the functioning of the heart exists without a heart attack. In other words, we can't use these for detecting latent coronary heart disease. These techniques, however, are extremely useful for other things—for example, for a wide variety of congenital heart disease, for some acquired diseases such as rheumatic heart disease and calcific aortic stenosis; these techniques are also very valuable for newly recognized but important forms of heart disease such as the mitral valve prolapse syndrome and asymmetrical septal hypertrophy, as well as such conditions as pericardial effusion. We are eagerly pursuing developments which will allow us to use such techniques for the recognition and quantitative assessment of lesions of the arteries so that we can recognize artery disease—and especially coronary artery disease—long before it results in symptoms. We are having some success in doing this in some of the major arteries of the extremities. These techniques have to be further developed before they become widely applicable, and very considerable developments have to be achieved before they are suitable

for such remote and relatively inaccessible vessels as the ones which nourish the heart.

ASPIRIN STUDY

Mr. MICHEL. You have an experiment ongoing as to whether regular aspirin ingestion can reduce the heart attack rate. What led you into this line of research, and are there any preliminary findings as yet?

Dr. LEVY. Several studies which gave preliminary evidence that regular administration of aspirin may be of benefit to patients with known coronary artery disease led to the development of the aspirin-myocardial infarction study [AMIS]. Dr. Hershel Jick and associates have published data comparing the prevalance of aspirin use in patients discharged from several hospitals. These data show a markedly lower use of aspirin in myocardial infarction group relative to the control group. A study by P. C. Elwood compared men with recent myocardial infarctions who were placed on aspirin or placebo. This trial shows an overall favorable effect of aspirin on mortality but the favorable effect was apparently confined to participants in one clinic. Groups of patients seen in the other participating clinics did not show a favorable effect for aspirin. A National Heart and Lung Institute sponsored study, the coronary drug project, ran a trial of aspirin and placebo in men with previous myocardial infarctions. Encouraging results from this trial, coupled with the other studies led to AMIS.

Recruitment of the 4,200 patients into AMIS is still in progress. Therefore, no preliminary findings are yet available.

Recruitment will be completed in the summer of 1976 and, with a 3-year followup, the study will end in the fall of 1979.

DIETARY FACTORS AND HEART ATTACKS

Mr. MICHEL. For years now, we have been listening to debates about diet and its relationship to coronary problems. Cholesterol is one example. With all this money we are spending, are we getting any closer to finding a direct tie-in between dietary factors and heart attacks? Could you illustrate some research currently underway directed toward this question?

Dr. LEVY. Yes, we are getting closer to finding a direct link between dietary factors and heart attack.

It has long been known that elevated serum cholesterol is a major risk factor in coronary heart disease. Likewise, it has been repeatedly demonstrated that one can alter serum cholesterol in individuals by manipulating diet. Populations which exhibit low heart attack rates also have been shown to subsist on relatively low saturated fat and cholesterol intakes. But it has been difficult to ascribe any or all of the differences in heart disease between these populations to diet because of the differences in genetic background.

An NHLI-funded epidemiological study of coronary heart disease in Japanese men living in Japan, Hawaii, and California was recently completed. The design of the study made it possible to study the relationship of environmental factors to coronary heart disease without the confounding effect of a genetic variable. It is significant that in this

study in which serum cholesterol, serum triglycerides and dietary intake were investigated, serum cholesterol was positively correlated with dietary intake of dietary cholesterol, saturated fat and animal protein. Serum cholesterol was negatively associated with complex carbohydrate intake. Another NHLI study of urban and rural Puerto Ricans in which the same parameters were measured is nearing completion. Results will show also a statistically significant correlation between dietary saturated fat and serum cholesterol levels and a negative correlation with complex carbohydrate intake in the urban group. This is the first time such a correlation has been demonstrated within a population.

A large collaborative survey of the prevalence of hyperlipidemia in populations in the United States, Canada, Israel, and the U.S.S.R. is now in progress. Dietary information has already been collected from 17,000 U.S. and Canadian participants and it is anticipated to collect such data from over 3,000 Israeli and 2,500 Soviet participants. A hallmark of this program is a highly standardized methodology. This is the first time such a large-scale multicentered collaborative population study, using absolutely comparable methodology, has been undertaken. It is hoped that with such large numbers, coupled with the comparability and precision of the measurements, the relationship of dietary factors to serum lipids will be elicited.

Whether lowering serum cholesterol in a population will also decrease the rate of heart attacks has not been shown definitively. Currently, two NHLI clinical trials are addressing this question. The multiple risk factor intervention trial is a program in which the three major risk factors—smoking, elevated serum cholesterol, and hypertension—are being modified in a population in which two or three of these factors are present. Serum cholesterol is being modified by diet. The Lipid Research Clinic's coronary primary prevention trial is a study in which serum cholesterol is being lowered by drug in a population exhibiting elevated serum cholesterol. These participants will be followed to see if such a regimen lowers the incidence of heart attacks as compared to a control group whose cholesterol remains elevated.

Thus, over the next 5 to 7 years, it is hoped that results from all these lines of research will clarify the role of diet in coronary heart disease.

HYPERTENSION

Mr. MICHEL. What is the nature and status of your hypertension research and how much money is being allocated to it?

Dr. LEVY. The majority—90 percent—of persons with high blood pressure are said to have "essential" or "primary" hypertension. Although the cause of essential hypertension is unknown and cannot be cured, blood pressures of patients with essential hypertension can be controlled. In only about 10 percent of persons with high blood pressure can any specific cause be identified. In some of these cases of "secondary" hypertension, once the underlying cause has been identified, the high blood pressure can be cured.

Our research program is attempting to learn the cause or causes of essential hypertension and, at the same time, is investigating new approaches to treatment. A widely held belief concerning the cause of essential hypertension contends that many factors are involved. Those

factors that initiate high blood pressure may not be those that sustain it, and factors of greatest importance at one stage of the disease may not be important during other stages.

The Institute currently supports about 200 research projects at universities and medical centers all over the country which are concerned with the etiology, pathogenesis, prevention, diagnosis, and treatment of all types 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 in Bethesda. I would like to highlight some of the principal research areas in our hypertension program.

We are supporting projects which search for causes of essential hypertension, and identification of genetic, environmental, and biochemical factors that increase susceptibility to the disease or aggravate its clinical course. Without such knowledge, cures or effective means of prevention are unlikely.

We are funding research on the evaluation of drugs and other therapeutic procedures for blood pressure control and assessment of the effects these measures have in reducing illness and death from hypertension and such complications as heart attacks, strokes, congestive heart failures, and kidney failure.

There are projects on the physiology and pharmacology of vascular smooth muscle.

Important research is being conducted on the role of kidney hormones, such as renin, kallikrein, and prostaglandins in blood pressure control and the interactions between the sympathetic nervous system and these hormones.

There are projects comparing surgical and medical treatment of renovascular hypertension and on the role of new mineralocorticoids in human and experimental hypertension.

We are also supporting research on the development of treatments for hypertension based on specific physiologic alterations.

Clinical trials are attempting to assess the effectiveness of antihypertensive therapy in controlling high blood pressure and to determine to what extent death and disability from the complications of hypertension can be reduced. The NHLI hypertension detection and followup program, established in 14 clinical centers, is following approximately 11,000 patients aged 30 to 69. 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 157,000 persons were screened to obtain these 11,000 participants. For those who have been observed 1 year or longer and have been seen within the last 4 months at the clinic, according to their latest record, 73 percent have achieved their goal blood pressure.

A second program, the multiple risk factor intervention trial, will evaluate the effectiveness of countermeasures against three cardiovascular disease risk factors, high blood pressure, elevated blood fats, and the cigarette-smoking habit, among high-risk males aged 35 to 37. Because high blood pressure often coexists with other risk factors, such combinations can sharply escalate the threat to the life and health of affected persons. 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 no risk factors. Recruitment of the approximately 12,000 study participants will be completed in 1976 and the clinical phase of the trial should be completed in 1981.

The amount allocated for these hypertension research activities is about $40 million.

NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM

Mr. MICHEL. You indicate that the national high blood pressure education program is working very well in educating the public about hypertension and stimulating them to seek treatment. Would you describe the nature of this program and describe in a little more detail the progress that is being made?

Dr. LEVY. The national high blood pressure education program is, we believe, a unique effort as a Federal program. It's mission is to reduce deaths and disability resulting from untreated high blood pressure through educational efforts directed at both the general public and patients as well as the health care providers. It completes our activity spectrum which includes basic research, clinical trials, and translation into practice. While educational efforts are not new to Government, the mandate for the National Heart and Lung Institute to coordinate rather than directly service the entire effort has produced an effective Federal-private interaction and cooperation. The result has been exceptionally successful leveraging of few Federal dollars by a factor which may be as high as 50 times.

The results have been heartening. Recent data suggests that, since the inception of the national high blood pressure education program, the number of persons unaware they have high blood pressure has dropped from nearly 50 percent to about 30 percent. The number of patients with good control of their high blood pressure has risen from about 15 percent to almost 30 percent. Both the total number of patient visits for hypertension and hypertensive heart disease and the data analysis is not complete, we believe we are seeing significant changes in the vigor and appropriateness of the therapy physicians are using to treat the condition.

We have no statistical data to present, but we do have indicators—from field visits, newspaper clippings, papers presented at professional meetings—that both the number and quality of effort of community programs is increasing.

The mechanisms we use are far too numerous to list here. The principles we follow are to identify and help others identify and mobilize resources already present in our health care delivery system. We meet regularly with key professionals, voluntary, industrial, and Federal groups to establish widely accepted uniform standards, and to synchronize efforts into a more concerted whole. We support research into educational methods so practitioners can more readily assist patients accept and maintain the lifelong treatment now required to control high blood pressure. In informal terms, we meet with any resource that will give us audience, present the nature of the problem and state-of-the-art steps that can be taken to address the problem, then ask people to raise their hand to accept some of the responsibility for making the solution happen.

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Mr. MICHEL. How much money are you allocating to this education program?

Dr. LEVY. We anticipate that the allocation in 1976 will be close to $3 million.

HEMOPHILIA

Mr. MICHEL. What is the nature of your hemophilia program and how much money is being devoted to it, directly and indirectly?

Dr. LEVY. The hemophilia program is a combination of fundamental and clinical research aimed at elucidating the process of blood clotting and the disruptions to this system which lead to so-called bleeding disorders. The hemophilias are a group of such disorders caused by an inherited deficiency of required clotting proteins. Fundamental research into the clotting mechanism has provided the groundwork for the recent improvements in hemophilia detection and treatment. Such advances may ultimately extend to prevention of the clinical expression of these disorders. Several of the clinical studies are exploring details of specific complications of hemophilia and their treatment. In addition, research on basic and technical aspects of plasma fractions for therapy is supported by the Division of Blood Diseases and Resources.

Blood clotting, or hemostasis, is a basic biological process of paramount importance. Disorders of this process may result in either bleeding or thrombosis. The hemophilia program includes research in all aspects of hemostasis, ranging from basic studies of molecular mechanism to specific clinical trials. Due to the complexity of this process, it is difficult to rigidly classify some research as "related" or "not related" to hemophilia. For example, in recent years, research on the hemophilias has been critical to work in thrombosis, and vice versa. This type of interaction is characteristic of a vibrant and productive scientific field.

The Institute is also participating closely with other agencies in the implementation of the hemophilia program portion of Public Law 94–63. The guidelines are being developed for establishing comprehensive hemophilia treatment centers, and the development of a blood separation centers program to supply necessary blood components and fractions for treatment of hemophilia. This is in conjunction with the Health Services Administration, the Hemophilia Foundation, and other interested groups. In addition to this advisory capacity, NHLI will initiate, shortly, a study of the criteria for component utilization and source material provision, which will form an analytical information base upon which to develop a program to improve capacity to provide adequate quantities of safe component and fractionation material at reasonable cost for the treatment of hemophilia.

The level of effort directed specifically at hemophilia is approximately $3.5 million. Additional efforts which relate to hemophilia indirectly, such as studies on the coagulation system itself, total approximately another $3.5 million.

RESEARCH COORDINATION

Mr. MICHEL. To what extent are you coordinating the various research efforts of your Institute with those of other institutes?

Dr. LEVY. The NHLI not only coordinates its research efforts with othe institutes, but with other Federal agencies, professional soci-

eties, voluntary organizations, and scientists in other nations. Major formal cooperation and collaborative efforts are being undertaken by NHLI. The Institute's national program with its broad, long-range goals provides an opportunity to stimulate efforts within and outside Government with groups which represent all sectors of society. The multiplier effect of this cooperation maximizes the Institute's resources and extends the national program well beyond its immediate sphere of influence.

The key formal mechanism for coordinating efforts related to the national program is the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources. This committee was established by the Secretary of the Department of Health, Education, and Welfare in November 1972, in accordance with the National Heart, Blood Vessel, Lung, and Blood Act of 1972. Chaired by the Director of the National Heart and Lung Institute, it coordinates Federal agency activities related to heart, blood vessel, lung, and blood diseases so as to assure their adequacy and technical soundness. The committee provides a forum for communication and exchange of necessary information. It consists of representatives not only from the other institutes, but from agencies of the Department of Health, Education, and Welfare, and from other departments and agencies of the Federal Government.

The NHLI, in cooperation with committee members, compiled and published an inventory of ongoing programs related to the national program in 1972 and 1973. Presently, this information is being updated to include 1974. The update has identified extensive research and study activities by committee member agencies which relate to the 23 major categorical disease problem areas included in the national program. These total more than 3,550 research projects, exclusive of those at NHLI.

Summary descriptions of the most important related programs were published covering 1972 and 1973 activities and the summary descriptions for 1974 are in press. These publications serve to improve communication and exchange of information on the national program not only among committee member organizations, but also among the scientific community in general. The volumes are widely disseminated within NHLI, the NIH, and other member departments and agencies of the committee as well as non-Federal organizations with missions related to the national program. This programmatic information assists Federal and non-Federal organizations to formulate plans and to implement and coordinate projects addressing the goals of the national program.

The information is also supplied to scientists and administrators at health professional schools, universities, colleges, and other institutions. It provides an extensive review of federally supported research in areas related to heart, lung, and blood diseases. These publications aid scientists and administrators in identifying the Federal funds available for various categories of research addressed by the national plan as well as which Federal departments and agencies administer these funds.

Plans have been developed for a further in-depth review of the complementary activities of the member departments and agencies of the committee. An intensive analytic effort is in its early stages. It

will identify, for each category within the NHLI program, the areas of gap, overlap, and duplication of efforts. Progress within each problem area will be evaluated against goals and objectives stated in the national plan. The aim of this review is to aid in the formulation of future policy as to the direction and scope of the committee members' collaborative efforts. Better collaborative efforts at the operational level are also envisioned as a result of this review.

A number of major cooperative and collaborative efforts have been implemented by each of the divisions of the National Health and Lung Institute. Examples of these efforts include coordination in blood resources, smoking, hypertension, nutrition, diabetes, pressure and underwater biomedical research, and sickle cell disease.

TRAINING

Mr. MICHEL. What is this "request pending" item of $20.9 million listed in your justifications which would be added to your regular fiscal year 1976 appropriation, bringing the total to $370 million?

Dr. LEVY. The "request pending" concerns the Institute's training programs. The National Research Service Award Act is the authorization by which training funds can be appropriated. Under this act, appropriations were authorized through fiscal year 1975. Renewal legislation providing authorization for fiscal year 1976 appropriations is pending. The $20.9 million is the amount contained for training in the fiscal year 1976 President's budget, and was not considered by Congress in the enactment of the fiscal year 1976 appropriations bill. The Institute has been able to meet its training program commitments in fiscal year 1976 under a continuing resolution.

NEW AND COMPETING RESEARCH GRANT COSTS

Mr. MICHEL. I note in the justifications you show the awarding of 335 "competing" grants in fiscal year 1976 for a total of $36 million, which averages out to around $100,000 each. Similarly, you have 429 "new" grants listed in 1976 at an average cost of $63,000 each, while in 1977 there are 29 listed at an average cost of $157,000. This appears to be a trend toward fewer but large grants. Is it, and if so, why?

Dr. LEVY. We have a unique situation in 1977 in regard to new research grants and grants competing for renewal. We have budgeted $23 million in 1977 for these grant categories. In 1971 the Congress provided funds to initiate specialized centers of research in arteriosclerosis and in pulmonary diseases. These are large multidisciplinary centers which look at both basic and clinical research. They have been a highly successful undertaking and are considered to be of highest priority. These grants are up for competitive renewal in 1977. We have, therefore, estimated that we would continue them at their current level of $18 million. In fact we are holding the competitive review now. We have received some 50 applications requesting $66 million of first-year funds. Some of these applications are from ongoing centers. Some are new requests from institutions which do not at present have centers. If we continue this center's program at its current level, we will have $5,059,000 left for regular research grant projects. We have estimated these at an average of $75,000 each for competing renewal grants in

1977 and $60,000 for new. This is the same average that is estimated for 1976. The trend toward fewer but larger grants is apparent only, not in fact. It is caused solely by the usual occurrence of this large block of centers changing from noncompeting status to "competing" new and renewal applications.

LARGE INCREASES

Mr. MICHEL. You are budgeting a 50-percent increase in rent, communications, and utilities. Why?

Dr. LEVY. The increase in rent, communications, and utilities is made up primarily of increased rental charges for building spaces from the General Services Administration, a 30-percent increase in postal rates, and increased FTS and commercial telephone charges.

Mr. FLOOD. Mr. Conte?

DECLINING DEATH RATE FROM CORONARY ARTERY DISEASE

Mr. CONTE. In the justification on page 77 you make an estimate that 14,000 Americans who would have died of coronary artery disease are now alive. To what do you attribute such a sharp decline?

Dr. LEVY. We are not entirely sure of the reasons and have to speculate somewhat. We believe that several factors are involved, rather than a single new effective measure. One of the factors is the fact that there has been no severe outbreak of influenza and pneumonia since 1968—at least until this year. We know that such epidemics can cause an increase of deaths among persons with underlying heart disease. A second factor appears to be improvement in the area of hypertension. The decline in mortality associated with both the acute and chronic forms of ischemic heart disease has been more pronounced for those who had associated hypertension than it has been for such heart attacks without associated hypertension. A third possible factor may be the 18.5-percent decrease in the number of men age 35 and over who smoke cigarettes reported between 1966 and 1970. Finally, we know that there is an increased use of foods with lower saturated fat content, but the national data do not indicate any shift in the mean cholesterol level of the general population. It is possible that some of the reduction in heart attacks is due to this dietary change, but we do not have solid evidence that this can be the major explanation.

Finally, and of great importance, over this decade there has been an explosive increase in our ability to diagnose and treat coronary artery disease and the acute events associated with heart attacks. These advances include the development of effective cardiopulmonary resuscitation—CPR—techniques outside the hospital as well as impressive technical electrical and pharmacologic advances in inhospital coronary care units.

DECLINING DEATH RATES—STROKE, HYPERTENSION, RHEUMATIC HEART DISEASE

Mr. CONTE. How much are the death rates for stroke, hypertension, and rheumatic heart disease declining?

Dr. LEVY. The death rate for stroke declined 16 percent in the past 6 years, hypertension declined 39 percent, and rheumatic heart disease declined 29 percent in the same period. In numbers of deaths, there

were 14,000 fewer deaths from strokes, 2,500 fewer deaths from hypertension, and 800 fewer rheumatic heart disease deaths in 1975 than in 1973.

PREVENTING SUDDEN DEATH AFTER HEART ATTACK

Mr. CONTE. Is your research going into the ways to prevent sudden deaths after a heart attack as well as the causes of the heart attack? I refer specifically to ways in which nonmedically trained people can aid one who suffers a heart attack.

Dr. LEVY. Yes; we have research looking into three key elements in the prevention of sudden death after heart atttack. First we are studying the reasons for the delay on the part of the person who suffers an attack before he calls for an ambulance or seeks medical help. We have found that in many cases the person has symptoms but does nothing about them, sometimes for hours. If we can get persons to recognize the signs of a heart attack and then to seek medical help we could cut down on the number of persons dying before they reach the hospital. This area of research involves the psychology of persons who have one attack and try to ignore or deny their symptoms, and also of persons who have not had a heart attack and don't want to admit that they are ill. The second area of research covers the period after the patient does call for an ambulance; a number of studies and demonstrations are underway to train and equip fire department and other emergency personnel to provide emergency treatment to heart attack victims while they are en route to the hospital. One example of this work is the Seattle Heart Watch. During the past 4 years an average of 100 lives a year have been saved in this out-of-hospital resuscitation program. If such emergency care could be extended to the entire country, it would save 40,000 or more lives a year. The third area in which recent and present research is saving lives is when the patient reaches the hospital. Coronary care units in many hospitals provide trained staff, sophisticated and automated monitoring and diagnostic equipment and effective medication that have made it possible for many patients to leave the hospital who would have died 5 or 10 years ago.

DIABETES AND HEART DISEASE

Mr. CONTE. How much emphasis are you putting on the possible link between diabetes and heart ailments?

Dr. LEVY. Diabetes mellitus has been clearly identified as an independent risk factor for coronary heart disease, sudden death, congestive heart failure, stroke, and peripheral vascular disease. The diabetic is twice as prone to heart disease and five times as prone to gangrene of the lower limb as the general population. At present the National Heart and Lung Institute supports somewhat more than $6 million of research directly related to the relationship of diabetes to heart and vascular disorders, and approximately $50 million more in studies of the metabolic mechanisms and disorders that are involved in both heart disease and diabetes. We have just launched a targeted effort to expand and intensify such research. We have issued a program announcement to medical schools and other research institutions encouraging them to submit research grant applications for studies of cardiac and vascular diseases in relation to diabetes. We have reason to believe that this expression of specific interest on our part will stimulate and hasten an even greater amount of research in this very important area.

SPECIALIZED CENTERS OF RESEARCH

Mr. CONTE. How successful are your specialized centers of research (SCOR)?

Dr. LEVY. The specialized centers of research programs—we call them SCOR's—was initiated in 1971 with four groups of centers addressing the disease areas of arteriosclerosis, hypertension, pulmonary diseases, and thrombosis. Our experience with the programs has demonstrated its value for highly original basic research for scientific communication, and for applied research in preventive and therapeutic medicine. Since the initiation of the national program the SCOR programs have expanded and developed further with a fifth group of SCOR's focusing on coronary or ischemic heart disease added in 1975.

The SCOR concept requires that each type of SCOR be a part of a national network of centers of research addressing similar problem areas and that there be close coordination among the centers within the network. To accomplish this active coordination, SCOR directors meet regularly to review progress, discuss common interests and problems, and plan collaborative efforts. Each SCOR also has a special collaborative relationship with the NHLI, working closely with the Institute staff to further appropriate NHLI goals as set forth in the national plan.

The hypertension and thrombosis SCOR's underwent a second round of competitive review for fiscal year 1976 funding. In 1977 the arteriosclerosis and pulmonary SCOR's will undergo similar competitive funding. The NHLI considers the continuation of the SCOR programs to be of the highest priority. Consequently, approximately $18 million, more than two-thirds of the funds budgeted in 1977 for all competing types of research grants, will be requird to maintain the arteriosclerosis and pulmonary SCOR's at their current level.

REDUCTION IN LUNG FUNDING

Mr. CONTE. Why is there an apparent deemphasizing of lung ailments by reducing this activity by $4,466,000?

Dr. LEVY. The overall Institute is being reduced. You may note that there is a reduction of $18,798,000 in heart and vascular diseases and $5,002,000 in blood diseases and resources, as well as the $4,466,000 cut in lung diseases. In each of our three major categorical areas the grant and contract availability is being reduced by 8.8 percent in 1977 from the 1976 appropriation level.

AMNIOCENTESIS

Mr. CONTE. I have read quite a bit about amniocentesis and it sounds like it could be very helpful. What are you doing to perfect and advance this technique?

Dr. LEVY. Amniocentesis has been in use for many years originally in connection with diagnosing and predicting the severity of RH disease in the fetus, a problem which has largely disappeared. However, there are many other applications, chiefly in genetic diseases where it is useful to know whether the fetus is potentially afflicted. The procedure itself is well standardized and safe. It is relatively easy to deter-

mine the sex of the fetus—important in such sex linked disorders as hemophilia, which affects only males—by chromosome analysis. More involved biochemical determinations are becoming possible for many metabolic diseases. Our Division of Blood Diseases and Resources has been particularly concerned with refining the diagnosis of sickle cell anemia at an early stage in fetal life. Research making possible the diagnosis from analysis of single red corpuscles is ongoing.

Amniocentesis may also prove to be a novel and provocative diagnostic breakthrough for detection of hyaline membrane disease during pregnancy. This technique of sampling amniotic fluid promises to result in exciting new therapeutic and preventive measures in the lung area as well. Surfactant material which is normally produced and secreted by the fetal lung is one of the substances composing amniotic fluid. Investigators have discovered that surfactant levels in amniotic fluid reflect the lung's ability to produce and secrete surfactant A rapid and easy test of surfactant in amniotic fluid has been developed. Studies are currently evaluating the reliability of this test and refining biochemical procedures for improving the accuracy of the diagnosis. The ability to predict hyaline membrane disease in the fetus by amniocentesis, which is a relatively safe procedure, permits the earliest possible available medical care for the newborn child and opens up new avenues of approach to this dread disorder by detecting prematurity of the infant and preventing immaturity of the lung.

HEMOPHILIA

Mr. CONTE. How much work is being done for the hemophilia problem?

Dr. LEVY. The hemophilia program is a combination of fundamental and clinical research aimed at elucidating the process of blood clotting and the disruptions to this system which lead to so-called bleeding disorders. The hemophilias are a group of such disorders caused by an inherited deficiency of required clotting proteins. Fundamental research into the clotting mechanism has provided the groundwork for the recent improvements in hemophilia detection and treatment. Such advances may ultimately extend to prevention of the clinical expression of these disorders. Several of the clinical studies are exploring details of specific complications of hemophilia and their treatment. In addition, research on basic and technical aspects of plasma fractions for therapy is supported by the Division of Blood Diseases and Resources.

Blood clotting, or hemostasis, is a basic biological process of paramount importance. Disorders of this process may result in either bleeding or thrombosis. The hemophilia program includes research in all aspects of hemostasis, ranging from basic studies of molecular mechanism to specific clinical trials. Due to the complexity of this process, it is difficult to rigidly classify some research as "related" or "not related" to hemophilia. For example, in recent years, research on the hemophilias has been critical to work in thrombosis, and vice versa. This type of interaction is characteristic of a vibrant and productive scientific field.

The Institute is also participating closely with other agencies in the implementation of the hemophilia program portion of Public Law

94–63. The guidelines are being developed for establishing comprehensive hemophilia treatment centers, and the development of a blood separation centers program to supply necessary blood components and fractions for treatment of hemophilia. This is in conjunction with the Health Services Administration, the Hemophilia Foundation, and other interested groups. In addition to this advisory capacity, NHLI will initiate, shortly, a study of the criteria for component utilization and source material provision, which will form an analytical information base upon which to develop a program to improve capacity to provide adequate quantities of safe component and fractionation material at reasonable cost for the treatment of hemophilia.

The level of effort directed specifically at hemophilia is approximately $3.5 million. Additional efforts which relate to hemophilia indirectly, such as studies on the coagulation system itself, total approximately another $3.5 million.

RATIO OF INTRAMURAL VERSUS EXTRAMURAL SUPPORT

Mr. CONTE. What is the ratio of intramural to extramural research?

Dr. LEVY. Included this year in the budget line "intramural research and direct operations" is not only our in-house intramural research laboratories and clinics but also most of the direct cost of administering our extramural programs. On page 87 of our justifications we have estimated that, of this, our intramural research programs for 1977 will total $28.4 million. This compares with $294.4 for our extramural programs, so that intramural research amounts to 8.8 percent of our total effort.

RESEARCH ON BLOOD COLLECTION AND STORAGE

Mr. CONTE. What sort of research is going on concerning collection and storage of blood and blood fractions?

Dr. LEVY. We are supporting research in the collection of whole blood, free of white blood cells, for the use in kidney transplantation with the hope of improving graft survival. At the present time we are also supporting extensive research in the storage and preservation of platelets and granulocytes, two of the cellular components of blood, both in the liquid phase and the frozen state. The work with platelets, which are essential to the clotting process, includes studies on defining optimal liquid storage conditions. The basic biochemical and physical properties of platelets, both in the liquid and frozen state, are also being investigated. The use of these various platelet preparations for transfusion in patients with low platelet counts is also under current investigation. Some ongoing studies are comparing different methods of collection. Investigations relating to the storage of granulocytes, the white blood cells important for combating infection, are being carried out. These studies are exploring novel freezing and thawing procedures. The NHLI is also supporting research in the collection of special plasma fractions for use in patients with specific deficiencies states.

NHLI FUNDING PATTERN

Mr. CONTE. In your professional judgment do you feel that this Institute is receiving its proper share vis-a-vis the other Institutes?

Dr. LEVY. The National Heart and Lung Institute has remained at about a constant 16 percent of the total NIH research budget since 1968. In fact the percentage of the NIH budget directed to heart research alone has fallen. With the passage of the National Heart, Blood Vessel, Lung, and Blood Act of 1972, the scientific community and the NHLI expected funding increases correlative to those received by the National Cancer Institute, an expectation not realized. Following the 1972 enactment, goals of a national program were established. Included in this program were large-scale clinical trials in arteriosclerosis, high blood pressure, and coronary heart disease. In 1972 and 1973 these trials were initiated. New programs were also developed in the lung area, as mandated. We also received new mandates in blood disease research and in blood resources as a result of the national blood policy, and, as you know the name of the Institute is about to be changed to include blood, which reflects additional responsibilities. There have been other new initiatives; of special note are the sickle cell disease program and the national high blood pressure education program.

We recognize that there have been budget increases in support of the Institute's programs; however, there has been an enormous expansion of our mission. At the moment we are resource, not idea, limited. In my professional judgment the NHLI could wisely invest an additional $100 million to $110 million in research and training in the heart and vascular, lung, and blood diseases and blood resources areas. However, I recognize that there are competing national priorities, competing for scarce resources, which must be considered by the administration and by the Congress.

Mr. FLOOD. Thank you, Dr. Levy. That will be all.

JUSTIFICATION OF THE BUDGET ESTIMATES

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

National Heart and Lung Institute

Amounts Available for Obligation [1/]

	1976	1977
Appropriation	$349,059,000	$342,855,000
Request pending	20,954,000	
Subtotal, adjusted appropriation	370,013,000	342,855,000
Comparative transfer from:		
"Office of the Director, NIH" (Transfer of Standard Level User Charges)	+334,000	
Total, obligations	370,347,000	342,855,000

[1/] Excludes the following amounts for reimbursable activities carried on by this account: 1976 - $140,000; 1977 - $140,000.

National Heart and Lung Institute

Budget Mechanism

(Dollars in Thousands)

	1976 Estimate			1977 Estimate		
	Number	FTE[1/]	Amount	Number	FTE[1/]	Amount
Grants						
Regular						
Non-competing.....	1,190		$140,000	1,527		$168,000
Competing.....	335		36,000	63		18,500
New.....	429		27,000	29		4,559
Supplemental.....	(145)		5,000	(125)		3,000
Sub-total.....	1,954		208,000	1,619		194,059
Special						
Research career program.....	203		6,000	184		5,500
Sub-total.....	203		6,000	184		5,500
Total grants.....	2,157		214,000	1,803		199,559
Fellowships						
Non-competing.....	478	478	7,415	107	409	7,636
Competing.....	---	---	---	---	---	---
New.....	76	190	3,000	---	---	---
Supplemental.....	---	---	---	---	---	---
Sub-total.....	554	668	10,415	107	409	7,636
Training grants						
Non-competing.....	125	500	10,539	48	192	5,152
Competing.....	---	---	---	---	---	---
New.....	---	---	---	---	---	---
Supplemental.....	---	---	---	---	---	---
Sub-total.....	125	500	10,539	48	192	5,152
Research & Development Contracts.....	350		87,659	300		82,000
Intramural Research and Direct Operations...			44,400			45,473
Program Management....			3,000			2,600
Standard level user charge.....			334			435
Total.....			370,347			342,855

1/ Full-time equivalent

DHEW - National Institutes of Health

CROSSWALK - 1976 Column 1977 Congressional Justification

INSTITUTE: National Heart and Lung Institute
(Dollars in thousands)

Program	Regular Program		Special	Training Programs		Research & Development	Intramural Research and	Program	
	Non-competing	Competing	Other	Grants	Fellowships	Contracts	Direct Operations	Management	Total
1. Heart and vascular diseases	$94,100	$40,900	$2,173	$7,377	$6,300	$63,688			$214,538
2. Lung diseases....	19,240	11,760	3,191	2,635	2,800	11,347			50,973
3. Blood diseases and resources....	26,660	15,340	636	527	1,315	12,624			57,102
4. Intramural research and direct operations.....	-						$44,734		44,734
5. Program management								$3,000	3,000
Total obligations	140,000	68,000	6,000	10,539	10,415	87,659	44,734	3,000	370,347

DHEW - National Institutes of Health

CROSSWALK - 1977 Column 1977 Congressional Justification

INSTITUTE: National Heart and Lung Institute
(Dollars in thousands)

Program	Regular Program		Special	Training Programs		Research & Development	Intramural Research and	Program	
	Non-competing	Competing	Other	Grants	Fellowships	Contracts	Direct Operations	Management	Total
1. Heart and vascular diseases	$107,000	$15,141	$1,950	$2,915	$4,046	$64,688			$195,740
2. Lung diseases....	25,000	9,559	3,000	1,783	1,765	5,400			46,507
3. Blood diseases and resources....	36,000	1,359	550	454	1,825	11,912			52,100
4. Intramural research and direct operations.....	-						$45,908		45,908
5. Program management								$2,600	2,600
Total obligations	168,000	26,059	5,500	5,152	7,636	82,000	45,908	2,600	342,855

Summary of Changes

1976 Estimated Obligations	$370,347,000
1977 Estimated Obligations	342,855,000
Net Change	-27,492,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Within-grade pay increases..	---	$300,000	---	+$300,000
2. Annualization of 1976 pay raise costs in 1977.....	---	800,000	---	+250,000
3. Wage board pay increase.....	---	100,000	---	+10,000
4. Federal Telecommunications System (FTS) rate increases.	---	204,000	---	+35,000
5. Bureau of Employment Compensation (BEC) rate inc....	---	30,000	---	+10,000
6. Postage rate increase.....	---	250,000	---	+50,000
7. Payment to the NIH Management Fund.....	---	14,757,000	---	+2,020,000
8. Standard level user charge..	---	334,000	---	+101,000
Subtotal.....	---		---	+2,776,000
B. Program:				
1. Research grants, for 429 new, 335 competing renewals, and 145 supplementals converted to noncompeting in 1977.....	---	140,000,000	---	+64,600,000
2. Research grants, for 29 new, 63 competing renewals, and 125 supplementals to be funded in 1977.....	---	68,000,000	---	+26,059,000
Subtotal.....				+90,659,000
Total, increases.....				+93,435,000
Decreases:				
A. Built-in:				
1. One less day of pay.....	---	17,623,000	---	-70,000
Subtotal.....				-70,000
B. Program:				
1. Research grants, for 427 noncompeting completed or converted to competing in 1977.....	---	140,000,000	---	-36,600,000
2. Research grants, for 335 new 429 competing, and 145 supplemental grants in 1976 completed or converted to noncompeting in 1977.....	---	68,000,000	---	-68,000,000
3. Research career program, a decrease of 19 grants in 1977.....	---	6,000,000	---	-500,000

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
4. Fellowships, for the completion of 259 full-time equivalent trainees.....	---	10,415,000	---	-2,779,000
5. Training grants, for the termination of 77 training grants, representing 308 full-time equivalent trainees.....	---	10,539,000	---	-5,387,000
6. Research and development contracts, for reductions in lung diseases and in blood diseases and resources programs.....	---	87,659,000	---	-5,659,000
7. Intramural research and direct operations, for position reductions and reductions in related costs.	672	44,734,000	-38	-1,504,000
8. Program management, for position reductions and reductions in related costs.	75	3,000,000	-5	-428,000
Subtotal.....			-43	-120,857,000
Total, decreases.....			-43	-120,927,000
Total, net change.....			-43	-27,492,000

Obligations by Activity

Page Ref.		1976 Rev. President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
78	Heart & vascular diseases.....	$172,643,000	$214,538,000	$195,740,000	-$18,798,000
81	Lung diseases.....	41,019,000	50,973,000	46,507,000	-4,466,000
84	Blood diseases & resources.....	45,952,000	57,102,000	52,100,000	-5,002,000
87	Intramural research & direct operations..	42,688,000	44,400,000	45,473,000	+1,073,000
	Positions	634	672	634	-38
89	Program management...	2,400,000	3,000,000	2,600,000	-400,000
	Positions	70	75	70	-5
	Standard level user charge.....	334,000	334,000	435,000	+101,000
	Total obligations	305,036,000	370,347,000	342,855,000	-27,492,000
	Positions	704	747	704	-43

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions..	747	704	-43
Full-time equivalent of all other positions.....	80	80	---
Average number of all employees.....	790	780	-10
Personnel compensation:			
Permanent positions.....	$13,463,000	$13,640,000	+$177,000
Positions other than permanent.....	1,350,000	1,450,000	+100,000
Other personnel compensation.....	460,000	480,000	+20,000
Subtotal, personnel compensation	15,273,000	15,570,000	+297,000
Personnel benefits.....	2,350,000	2,380,000	+30,000
Travel and transportation of persons.	761,000	785,000	+24,000
Transportation of things.....	140,000	155,000	+15,000
Rent, communications and utilities...	1,100,000	1,636,000	+536,000
Printing and reproduction.....	500,000	500,000	---
Other services:			
Project contracts.....	84,659,000	79,000,000	-5,659,000
NIH Management Fund.....	14,757,000	16,777,000	+2,020,000
Other.....	7,353,000	5,505,000	-1,848,000
Supplies and materials.....	4,300,000	4,100,000	-200,000
Equipment.....	1,200,000	1,100,000	-100,000
Grants, subsidies, and contributions.	237,954,000	215,347,000	-22,607,000
Total, obligations by object.....	370,347,000	342,855,000	-27,492,000

Significant Items in House and Senate Appropriations Committee Reports

Item	Action to be taken
1976 House Report	
1. The Committe believed that for maximum effectiveness in treating hemophilia and other blood diseases, emphasis should be given to research on the blood delivery systems, as well as the improvement of blood fractionation processes. (Page 27)	1. Improved management of the national blood system is a major goal of the NHLI. To optimize utilization of blood resources the Institute is developing new technology, methods, and procedures in collaboration with the Office of Bureau of Biologics (FDA) and the Health Resources Administration (HRA) within government and the American Blood Commission (ABC) in the private sector. The NHLI participated in the formation of the ABC during 1974 and 1975 and has contracted with the ABC for several task forces whose efforts will have a major impact in providing the data upon which the Commission will implement the goals of the National Blood Policy.
2. The Committee recommended that a survey of blood research be developed so that the Congress may have a better overview of the opportunities available. (Page 28)	2. The NHLI has (1) contracted for an independent study on on-going blood research throughout the NIH and how these programs could be coordinated. The results of this study will be available in the very near future. (2) The Blood Diseases and Resources Advisory Committee is currently reviewing in depth the entire blood research and resources field, what the impact of the National Program has been to date, and what are future needs and opportunities. Their report will be available before the end of this fiscal year.
3. The Committee believed that an inter-Institute committee should be developed to coordinate information on blood research. (Page 28)	3. An Interagency Coordinating Committee has been established within the Office of the Assistant Secretary for Health for the implementation of the National Blood Policy and the operation of the American Blood Commission. There has also been established a Hepatitis Policy Committee and a Hepatitis Liaison Committee with the NIH, the Food and Drug Administration, the Department of Defense, and the Veterans Administration. The NHLI study of blood research throughout the NIH mentioned in the paragraph above is expected to provide the basis for an inter-Institute committee on blood research.

House Report (continued)

4. The Committee expects NHLI to use a portion of the increased funds to expand its diabetes research program and coordinate this program with the other NIH Institutes in accordance with the National Diabetes Mellitus Research and Education Act. (Page 28)

4. The Act called for the establishment of a National Commission on Diabetes to draw up a plan for a coordinated research program in diabetes. The Directors of the seven NIH Institutes concerned with diabetes were appointed to the Commission. Ten representatives of the non-Federal sector which is formulating a long-range plan for National Program of research, education, and treatment in diabetes mellitus. The Act also authorized the Diabetes Coordinating Committee, chaired by the Director of NIH and consisting of the same seven NIH Institute Directors as well as representatives from all Federal departments and agencies whose programs involve health functions or responsibilities related to diabetes. NIAMDD is the lead Institute of this committee which provides background information to the Commission and is preparing a report for submission to Congress. The NHLI has a strong commitment to diabetes research and control. The metabolic effects and cardiovascular consequences of diabetes are studied as aspects of NHLI supported investigations focused on atherosclerosis, hypertension, arrhythmias, heart failure, shock and thrombosis in man and animals. In addition, epidemiological investigations of coronary heart disease include studies of diabetes as one of the several predisposing risk factors.

1976 Senate Report

1. The Committee feels that on the basis of promising laboratory and clinical studies an expanded program for protecting jeopardized heart muscle should be launched. (Page 39)

1. NHLI plans to conduct a collaborative study to evaluate one or more techniques to protect ischemic myocardium and minimize the size of the ultimate infarct associated with acute heart attack. This is an extension of preliminary studies conducted over the past four years.

Authorizing Legislation

Legislation	1977 Authorized	1977 Appropriation Requested
Public Health Service Act, Title III, Part A, Section 301--Research and Investigation, In General.....	Indefinite	$342,855,000
Title IV, Part B--National Heart and Lung Institute.....	1/	
Title IV, Part I--National Research Service Awards.....	1/	
Title XI--Genetic Blood Disorders.....	1/	

1/ Authorizing legislation expired June 30, 1976. Extension legislation is pending.

National Heart and Lung Institute
Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	329,059,000	379,059,000	
Items not considered		(20,954,000)	(20,954,000)	
1977	342,855,000			

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 as authorized by P.L. 93-192.

Note: The figures presented in this table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of general research support grants is not the function of this Institute in 1977. The amount originally contained in previous years for this particular program has been removed for comparability purposes.

National Heart and Lung Institute

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	329,059,000	379,059,000	
Items not considered		(20,954,000)	(20,954,000)	
1977	342,855,000			

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 as authorized by P.L. 93-192.

Justification

National Heart and Lung Institute

	1976 Rev. President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Heart & vascular diseases.....	$172,643,000	$214,538,000	$195,740,000	-$18,798,000
Lung diseases.....	41,019,000	50,973,000	46,507,000	-4,466,000
Blood diseases & resources.....	45,952,000	57,102,000	52,100,000	-5,002,000
Intramural research & direct operations..	42,688,000	44,400,000	45,473,000	+1,073,000
(Positions).....	(634)	(672)	(634)	(-38)
Program management...	2,400,000	3,000,000	2,600,000	-400,000
(Positions).....	(70)	(75)	(70)	(-5)
Standard level user charge.....	334,000	334,000	435,000	+101,000
Total obligations	305,036,000	370,347,000	342,855,000	-27,492,000
(Positions)	(704)	(747)	(704)	(-43)

General Statement

A generation ago, the Federal Government launched a fledgling research enterprise aimed at reducing the terrible toll exacted by diseases of the heart, lungs, blood vessels, and blood. Now known as the National Heart and Lung Institute, it has matured into the most influential and respected research program of its kind in the world. Through the efforts of the Institute's own internal research and of the scientists it has supported elsewhere, basic comprehension of these diseases has doubled and redoubled time and time again. In 1972 the National Heart, Blood Vessel, Lung, and Blood Act expressed the determination of the President and the Congress to lessen the human suffering and financial burden caused by CV, pulmonary, and blood diseases and to improve the utilization of nation blood resources. One result of this Act was the formulation of a National Program involving many interlocking relationships. The Institute, with the advice of the National Heart and Lung Advisory Council, other advisory committees, and the scientific community, has utilized its 27 years of accumulated expertise to create a many-faceted, well-integrated scientific effort to help relieve the American people of the burdens imposed by these diseases. New initiatives undertaken since passage of the Act include the Specialized Centers of Research, the Lipid Research Clinics, several major clinical trials, and the emerging National Research and Demonstration Center program. The combination of these targeted programs, together with a wide range of investigator-initiated research, have resulted in a dynamic and effective National Program.

The NHLI has also fostered practical advances in the prevention and treatment of these diseases to speed newly acquired knowledge into the mainstream of clinical medicine. There are newly initiated prevention and control activities in hypertension, arteriosclerosis, sickle cell disease, emergency treatment of cardiac and respiratory failure, recognition and treatment of neonatal respiratory distress syndrome (hyaline membrane disease), and rehabilitation of heart attack victims. In addition, the National Research and Demonstration Centers each have major prevention, control, and education programs.

And now, for the first time, there is strong evidence of the most welcome news of all--that the relentless march of ever-increasing mortality has been halted and perhaps even thrown back in the major disease categories. By conservative estimate, 14,000 Americans who would have died of coronary artery disease last year are now alive. And the death rates from stroke, hypertension, and rheumatic heart disease are definitely declining.

Heart and Vascular Diseases

	1976 Rev. President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Subactivities:				
Arteriosclerosis.....	$49,721,000	$61,787,000	$56,373,000	-$5,414,000
Hypertension.....	30,385,000	37,759,000	34,450,000	-3,309,000
Cerebrovascular disease	3,280,000	4,076,000	3,719,000	-357,000
Coronary heart disease	37,636,000	46,769,000	42,671,000	-4,098,000
Peripheral vascular diseases.....	3,453,000	4,291,000	3,915,000	-376,000
Arrhythmias.....	13,121,000	16,305,000	14,876,000	-1,429,000
Heart failure & shock	12,775,000	15,876,000	14,485,000	-1,391,000
Congenital and rheumatic heart diseases.	7,424,000	9,225,000	8,417,000	-808,000
Cardiomyopathies and infections of the heart.....	2,590,000	3,218,000	2,936,000	-282,000
Circulatory asssistance	12,258,000	15,232,000	13,898,000	-1,334,000
Total.....	172,643,000	214,538,000	195,740,000	-18,798,000
Budget Mechanism:				
Research Grants:				
Regular:				
Non-competing....	94,100,000	94,100,000	107,000,000	+12,900,000
Competing.....	24,065,000	40,900,000	15,141,000	-25,759,000
Special.....	2,000,000	2,173,000	1,950,000	-223,000
Subtotal.....	120,165,000	137,173,000	124,091,000	-13,082,000
Fellowships.....	4,195,000	6,300,000	4,046,000	-2,254,000
Training grants.....	5,800,000	7,377,000	2,915,000	-4,462,000
Research & development contracts.....	42,483,000	63,688,000	64,688,000	+1,000,000
Total.....	172,643,000	214,538,000	195,740,000	-18,798,000

The NHLI seizes and exploits opportunities in ways that determine the directions of cardiovascular research in this country. One example is the dramatic shift in the emphasis of cardiovascular studies beginning in the late 1960s. It was triggered by the establishment of the institute's Myocardial Infarction Research Units. Myocardial infarction is the damaging or death of an area of the heart muscle (myocardium) resulting from a reduction in the blood supply reaching that area.

At the time the NHLI set up the units, the major trend in cardiovascular research was to concentrate on congenital heart disease, diseases of the valves of the heart, and pulmonary hypertension. Atherosclerosis was being studied, but the acute heart attacks, often catastrophic, that result from it were largely ignored. The condition of a patient was seen as too precarious to permit investigation, and the outcome was considered inevitable--one way or the other.

More than 80% of all deaths from heart disease were attributable to myocardial infarction. Yet less than 1% of the NHLI's research support was directly applicable to the study of this disease in man. Clearly there was urgent need for research on this disease killing these people.

Through the intervention and encouragement of the NHLI's Myocardial Infarction Research Units, research in this area was stimulated throughout the country. Within five years, there was a 10-fold jump in papers and abstracts reporting research results--an accurate indicator of effort. And now it is proving its worth. Fundamentally new concepts and approaches have emerged. It has become apparent that the size of the infarct, the dead heart tissue, is not irreversibly predetermined when a patient enters a hospital with a heart attack. The amount of heart muscle damaged or destroyed may hang in the balance for several days. This discovery, in turn, has stimulated efforts to find ways of measuring the infarct's size. Several methods of treatment that reduce the ultimate size of the injury have been shown to be effective in experimental animals. Preliminary results in man offer the first real hope of reducing the cardiac damage of a heart attack, a step that would assure a fuller life for more survivors.

Still new avenues are opening. It has become clear that research attacks must also be directed to the early stages of atherosclerosis--long before the arteries are nearly totally obstructed. Suddenly long-cherished concepts of coronary artery disease are being questioned, and promising new approaches to prevention and treatment are being suggested. Platelets and other components involved in blood coagulation are being examined with new interest because of their role in the disease. Similarly, old shibboleths about the inevitability of sudden cardiac death have been rejected. There is now convincing proof that a large percentage of "sudden death" victims can be revived by prompt resuscitation. Basic disease processes of sudden death must now be understood for design of the most effective ways of combatting it.

Indeed the Institute realizes that continuing need for the highest priority is to develop the new knowledge which will enable the better understanding of the fundamental processes involved in all the heart and vascular diseases. Such knowledge is the prerequisite for prevention and rational treatment, and examples are the unraveling of the pathophysiology of the arteriosclerosis process, heart failure, rhythm conduction in the heart, etc. No central authority can establish predetermined guidelines to obtain such knowledge. In the main it can only be developed by individual investigators, working in small or large groups, following their own leads, and pursuing problems of their own choosing. History bears out the importance of such basic non-directed research and our current level of knowledge and understanding has been provided, in large part, by the fruits of this non-directed research.

The ultimate emphasis must be placed on the primary prevention of heart diseases, which cost the nation's economy over $40 billion and take one million lives each year, or over half the nation's deaths. All too often the first sign of arteriosclerotic heart disease is heart attack, stroke, or even worse, sudden death. These sequellae must be prevented by learning more about the basic processes and mechanisms that cause them. There must be developed better noninvasive diagnostic techniques to detect them. There must be evaluated new therapies to prevent them.

Premature atherosclerosis and hypertension two of the major problem areas in the NHLI National Program, are the sequelae of diabetes. Indeed diabetes can find expression in most of the heart programs, and NHLI has a strong commitment to diabetes research and control. Programs include the metabolic effects and CV consequences of diabetes on atherosclerosis, hypertension, coronary heart disease, peripheral vessel disease, arrhythmias, heart failure and shock, and thrombosis. In addition, epidemiological investigations of coronary heart disease include studies of diabetes as one of the several predisposing risk factors.

NHLI-supported research has been instrumental in important progress in understanding and treating hypertension--the serious and silent disease that afflicts 23 million Americans. Specific forms of hypertension can now be detected so that more effective treatment can be offered, a key advance in the control of the disease.

But there is a paradoxical situation in hypertension that leaves it a major unresolved health problem for most patients. Since hypertension is most often symptomless, medication usually offers no relief that is evident to the patient. But the drugs often have unpleasant side effects. So instead of feeling fine, as before the hypertension was diagnosed, the patient, after being forced to buy expensive drugs, doesn't feel well any more. Many patients rebel and simply refuse to take the medication.

Still, more basic research into the causes of hypertension is needed to help devise a solution to the problem of the disease that is less expensive than current medication and more acceptable to the patient. Also, the NHLI intends to undertake intensive epidemiological research to seek causal factors for hypertension developing at young age with particular emphasis on determining differences in the Black population compared to non-Black persons. Hypertension occurs three times more frequently in Blacks than in non-Blacks in this country. Here screening, education, and follow-up programs may well result in a major payoff in saving lives for Black people.

The essential final test of the effectiveness of promising research findings and clinical hypotheses is a controlled clinical trial in man. The NHLI is engaged in a number of such trials which are both complex and expensive. They involve many investigators in a large number of medical centers and they require long-term commitments of a considerable portion of the Institute's budget for successful completion. Given limited resources, the Institute must continually evaluate the cost-effectiveness of on-going trials and it must consider even more carefully any additional commitment to new trials that may be occasioned by new research hypotheses requiring definitive testing in man.

In 1971 the NHLI initiated its first series of Specialized Centers of Research (SCOR) including the disease areas of arteriosclerosis and hypertension. In 1975 another group of centers, focusing on coronary or ischemic heart disease was added to this program. Half a decade of experience with the SCOR program has demonstrated its value for highly original basic research, for scientific communication, and for applied research in preventive and therapeutic medicine. Now underway is competitive solicitation for renewal or new arteriosclerosis centers in 1977, which should further invigorate this program.

Lung Diseases

	1976 Rev. President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Subactivities:				
Structure and function of the lung	$12,183,000	$15,139,000	$13,813,000	-$1,326,000
Pediatric pulmonary diseases	6,768,000	8,410,000	7,764,000	-736,000
Emphysema and chronic bronchitis	4,881,000	6,066,000	5,534,000	-532,000
Fibrotic and immunologic lung diseases	6,522,000	8,105,000	7,395,000	-710,000
Respiratory failure	7,794,000	9,685,000	8,836,000	-849,000
Pulmonary vascular diseases	2,871,000	3,568,000	3,255,000	-313,000
Total	41,019,000	50,973,000	46,507,000	-4,466,000
Budget Mechanism:				
Research grants:				
Regular:				
Non-competing	19,240,000	19,240,000	25,000,000	+5,760,000
Competing	7,615,000	11,760,000	9,559,000	-2,201,000
Special	2,060,000	3,191,000	3,000,000	-191,000
Subtotal	28,915,000	34,191,000	37,559,000	+3,368,000
Fellowships	1,851,000	2,800,000	1,765,000	-1,035,000
Training grants	2,547,000	2,635,000	1,783,000	-852,000
Research and development contracts	7,706,000	11,347,000	5,400,000	-5,947,000
Total	41,019,000	50,973,000	46,507,000	-4,466,000

Without the support of the NHLI, research into the lung would be abruptly curtailed. Instead, it is a field of ever-increasing excitement and promise, much of which stems from new concepts of the lung's function. Traditionally the lung has been viewed as the breathing organ--pure and simple. Now research is showing that the lung releases important hormones and active chemical mediators. It also transforms other biologically active compounds in the blood that are important not only to disorders of the lung, but to diseases of other organs as well.

From this work has emerged new research leads into hypertension, asthma and other allergic diseases, and into the lung ailments brought on by drugs, smoking and environmental hazards.

Knowledge of the lung does not yet provide sufficient foundation to put great emphasis on the improvement of treatment. Therefore, by design, the Lung Division has devoted most of its energies to basic research. Priority has properly gone to acquiring detailed knowledge of the structure of the lung, the types of cells that make it up, the functions of the lung other than breathing, the nature, composition and functions of pulmonary and bronchial secretions, and the causes and mechanisms of diseases of the lung. These findings are laying the needed foundation for clinical advances of the future.

The lung has many different types of cells, more different types than most other organs. The task of research has been to systematically discover the role of each cell type in order to fully understand how the lung works and how disorders impair it. As a major first step, the type of cell of the air sacs of the lung has been identified, isolated and grown in a test tube. This cell type is of special interest because it is the one principally involved in repair of damaged lung and it is the cell type that manufactures pulmonary surfactant. Abnormality of surfactant is the precipitating factor in hyaline membrane disease (the dread neonatal respiratory distress syndrome of the newborn). This is among the most important lung disorders of childhood. About 40,000 babies are born each year with hyaline membrane disease, the largest single cause of death in the newborn in the U.S. Many of these will die unless given prompt treatment, presently unavailable except in a few specialized facilities.

Research revealing ways of assessing, before birth, the degree of maturation of fetal lungs through the technique of amniocentesis--removal of amniotic fluid with a needle--has been useful in detecting incipient hyaline membrane disease and preparing for it.

The studies into basic understanding of fetal lung maturation have also shown that some diseases of the mother, such as diabetes, act to retard fetal lung growth. It has also been discovered that corticosteroids given to these mothers accelerate fetal lung growth. So plans are under way to begin a controlled clinical trial of corticosteroid therapy for pregnant women--when tests show their babies will be born with hyaline membrane disease--to see it current use of the drug to accelerate fetal lung growth is justified.

The discovery--through support of the National Institute of Allergy and Infectious Diseases--of a new class of immunoglobulins (any one of the proteins of animal origin having known antibody activity) nine years ago gave solid foundation for the first time to the concept that hay fever and asthma were allergies. Studies jointly supported since by the NHLI and NIAID have attacked asthma on a fundamental level and promise a more rational approach to asthma in the future.

Research shows that lymphocytes from asthmatics contain abnormally low levels of cyclic AMP, the recently discovered natural mediator, and a way has been found to bring the levels up to normal. Concurrently, successful establishment of animal models for asthma in dogs and monkeys should enable system-

atic evaluation of new drugs and techniques without risk to man.

The fact that these important results come from related studies in two institutes of the NIH well illustrates the continual interdependency of the NIH programs.

It has only been a decade since a specific hereditary enzymatic defect was shown to be associated with one form of emphysema. This discovery gave an entirely new dimension to the understanding of emphysema and lung biology in general. Current research is designed to reveal the precise role of this defect in the overall problem of chronic obstructive pulmonary disease. Still more exciting is the fact that investigators are beginning to define the role of other enzymes in the onset of emphysema, studies that may provide a basis for prevention of the disease.

Important clinical research has shown that improved care for underweight newborn infants, including preventive measures and mechanical breathing assistance, appears to have resulted in significantly higher IQs for these children--with or without hyaline membrane disease--compared with such children in the past. The benefits that may arise from this study are incalculable.

Seventeen Pulmonary Specialized Centers of Research (SCORs) (see justification under Heart and Vascular Diseases) are being supported by the Institute. They are concerned with basic and clinical research on various aspects of pulmonary disease. Over the past few years research into pulmonary disease has increased and the new interdisciplinary approaches that characterize the SCOR grant are now emphasized in several areas of the Institute's National Program Plan. A new open competition for Pulmonary SCORs was announced in May 1975. The new or renewed Plumonary SCORs (to be funded in 1977) will address one of the four disease categories requiring further emphasis; namely, chronic diseases of airways, pediatric pulmonary diseases, fibrotic and immunologic pulmonary diseases, and pulmonary vascular diseases.

The National Research and Demonstration Center in pulmonary diseases (see justification for Heart and Vascular Diseases for definition and scope of such Centers) concentrates on lung diseases, with special emphasis on occupational pulmonary disease resulting from prolonged exposure to harmful dust and fumes in various industries and occupations.

Blood Diseases and Resources

	1976 Rev. President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Subactivities:				
Bleeding and clotting disorders	$16,864,000	$20,956,000	$19,121,000	-$1,835,000
Biomaterials	3,860,000	4,797,000	4,376,000	-421,000
Sickle cell disease & related disorders of the red blood cell.	14,200,000	17,645,000	16,099,000	-1,546,000
Blood resources	11,028,000	13,704,000	12,504,000	-1,200,000
Total	45,952,000	57,102,000	52,100,000	-5,002,000
Budget Mechanism:				
Research grants:				
Regular:				
Non-competing	26,660,000	26,660,000	36,000,000	+9,340,000
Competing	7,356,000	15,340,000	1,359,000	-13,981,000
Special	350,000	636,000	550,000	-86,000
Subtotal	34,366,000	42,636,000	37,909,000	-4,727,000
Fellowships	1,945,000	1,315,000	1,825,000	+510,000
Training grants	712,000	527,000	454,000	-73,000
Research & development contracts	8,929,000	12,624,000	11,912,000	-712,000
Total	45,952,000	57,102,000	52,100,000	-5,002,000

Blood diseases such as sickle cell anemia have been an official responsibility of NHLI programs only since 1972. However, the NHLI had been supporting basic and clinical research into a broad range of blood diseases long before, and perhaps the most dramatic story of basic studies emerging into patient care has been with hemophilia.

The treatment of hemophilia A (factor VIII) deficiency was revolutionized by the development of new procedures for preparation of factor VIII. This, and related NHLI supported advances have helped improve clinical management of hemophilia and to permit a fuller life for those afflicted with the disease. More recently, a greater understanding of the nature of factor VIII, and of bleeding disorders related to it, have emerged from the research laboratory. These results should pave the way for more precise treatment of hemophiliacs. For example: (1) more precise diagnosis of related disorders, such as von Willebrand's Disease, promises to make therapy more effective; (2) diagnosis of carriers of hemophilia can be detected more accurately; (3) factor IX preparation, for treatment of hemophilia B, has been improved.

A major problem for a goodly number of hemophiliac patients is the development of so-called factor VIII inhibitors--antibodies which can interfere with the efficacy of treatment. A collaborative study has been initiated by NHLI to determine the occurrence, nature, and significance of these inhibitors and to find ways to prevent and overcome them.

The obverse of the problems associated with bleeding is the problem of abnormal clotting and the resulting occlusion of blood vessels in various parts of the body, in other words, thrombosis.

The Institute supports five Thrombosis Specialized Centers of Research (SCORs) (for definition see justification for Heart and Vascular Diseases) to focus resources, facilities, and manpower on the improvement of diagnosis, treatment, and prevention of thrombosis. The program is concerned with the elucidation of the pathogenesis of thrombi and the study of promising observations and interventions. This program is being renewed in 1976.

A specific approach that offers considerable promise in the prevention of post-operative thrombosis is the use of small amounts of heparin, an anti-clotting factor. Pulmonary embolism is a fatal complication of surgery in an estimated 5,000 to 10,000 patients per year. Such emboli arise from clots (thrombi) in leg and pelvic veins. Recent studies have demonstrated that the development of such thrombi can be markedly inhibited by administration of low doses of heparin before, during, and after surgery. This preventive approach holds great promise--it has been made possible by increased understanding of the coagulation mechanism and improved diagnostic techniques. The fundamental research leading to these advances has been extensively supported by NHLI. Such research, as well as pertinent clinical trials, are high priority items.

In basic research on blood diseases, a cell-free system for protein synthesis has been developed enabling the study of human genetic defects in the test tube. Experiments have shown that portions of the human genetic code involved in sickle cell and other hemoglobin defects will be successfully copied by the subcellular genetic translation machinery of red blood cells of rabbits. It is hoped that this pioneering work will lead to biochemical scrutiny of the protein-synthesizing machinery in other kinds of human disease.

Basic research on sickle cell and other abnormal hemoglobins has been underway for many years, much of it supported by the NHLI, and a vast amount of biochemical information has been accumulated. Clinical research, however, has been much more limited, largely reserved to the bare description of cases. Even the natural history of the disease needs further study.

Specific therapy for sickle cell disease does not exist. Several leads are being pursued that would alter the structure or function of the sickle hemoglobin itself, or the red cell membrane, to inhibit sickling. Most of these studies are in early phases, however, and clinically useful results are but distant possibilities.

A micro-column chromatography procedure has been developed which can identify the hemoglobin type(s) of a single cell. Further refinement of this method will aid in prenatal identification of sickle cell disease. The method is also being field-tested for its ability to identify the carrier state of Cooley's anemia.

The Division is also concerned with research and development pertaining to the national blood resource. Over the past 30 years, our national blood resource has grown rapidly, especially in the number and size of organizations involved in the collection, processing, and distribution of blood and blood products, and it has become large, diverse, and fragmented. The problems of replacement, wastage, inefficient usage and lack of adequate regulation resulted in the development of a National Blood Policy in July 1973 by the Department of Health, Education, and Welfare, designed to assure an adequate supply of high quality blood and blood products to everyone in need and to encourage its efficient use.

The implementation of the National Blood Policy was entrusted to the American Blood Commission (ABC) with the intent of letting the private sector resolve the issue. The NHLI is committed to the support of task forces established by the ABC for such specific purposes as the creation of a national data center pertaining to

all aspects of blood banking; the development of a national plan for regulation of the blood supply throughout the country; the study of optimal methods of donor recruitment and donor motivation. An additional aim of one of these task forces will be the development of criteria and methods for the efficient utilization of the blood resource.

Considerable progress has been made in separating whole blood into its various components (red cells, platelets, white cells, plasma, and plasma fractions such as albumin, the antihemophilic factor, and globulins used for the treatment of viral and other infections). Research and educational efforts are underway to improve methods of separation, the quality of components, and the development of specific blood component therapy. A major problem associated with blood transfusions is hepatitis which annually accounts for about 850 deaths and 17,000 cases of the disease in recipients of human blood. The NHLI actively supports research aimed at reducing the hepatitis risk. These efforts include a large collaborative study of the epidemiology of the disease. The Institute also supports a program including research on chimpanzees, the only susceptible animal species.

The search for alternate approaches to meeting our blood needs was precipitated by: (1) increased demand on the national blood resources, (2) risk of hepatitis in transfusions, (3) problems of storing blood, and (4) problems of providing compatible blood.

Plasma can be replaced by albumin (itself derived from plasma) and by a number of other compounds such as dextran, gelatin, etc. These can be used to treat acute blood loss and shock caused by reduced blood volume, but they lack the ability to carry oxygen. The Institute supports extensive research in blood substitutes, especially synthetic chemicals called fluorocarbons, which like red corpusles, can carry oxygen and hold considerable promise. The current program is aimed at the synthesis of new and more fluorocarbons and their testing in animals and ultimately in human volunteers.

The National Research and Demonstration Center for blood resources (see justification for Heart and Vascular Diseases for the definition and scope of such centers) is mainly concerned with improvement of procedures for the acquisition, processing, storage, distribution, and clinical use of blood and blood products.

Intramural Research and Direct Operations

	1976 Rev. President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Intramural Laboratory & Clinical Research.....	$26,464,000	$27,686,000	$28,412,000	+$726,000
(Positions).....	(383)	(406)	(383)	(-23)
Direct Operations.....	16,224,000	17,048,000	17,496,000	+448,000
(Positions).....	(251)	(266)	(251)	(-15)
Total.....	42,688,000	44,734,000	45,908,000	+1,174,000
(Positions).....	(634)	(672)	(634)	(-38)

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 1976 and 1977. The dollar change indicated is for "built-in" increases, primarily an increase in the NIH Management Fund reimbursement.

Within the frame work 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 long been recognized for the excellence and productivity of its cardiovascular laboratories. Until 1972 its own laboratories had not engaged in pulmonary research. Primary goals for the new lung program were to understand the biochemical processes underlying the normal maintenance of lung tissue and how these processes are altered in lung disease. Major emphasis is placed upon understnading the connective tissue "cement" that bands together the cellular components of lung. One of these components, collagen, is the most abundant protein in lung, comprising 10 to 15 percent, by weight, of normal lung tissue in adults. NHLI studies concerned with learning more about the composition, synthesis, and destruction of lung collagen have indicated that the lung produces as many as four different forms of this material.

Methods developed in NHLI have resulted in the isolation of several different types of lung cells which can now be maintained in tissue culture. Recent studies indicate that collagen molecules are produced and secreted by these different lung cells. In addition to producing collagen, studies show that lung cells also have enzymatic mechanisms to destroy excess or poorly formed collagen. 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.

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 for this purpose are the membrane oxygenators developed by the Intramural Program. Their gentle blood-handling characteristics make them suitable for providing respiratory assistance over long periods--up to a week or more in several reported instances--by which time many acute respiratory crises have run their course.

This oxygenator is now in clinical use as a safe and reliable support for whatever length of time is necessary to see the patient through an acute respiratory

crises. Its basic configuration has now been adapted to control excessive carbon dioxide hypercapnia in patients.

NHLI scientists have developed methods for casting very thin membranes without the pinhole defects that have been the chief cause of membrane failure in oxygenators. Flawless silicone rubber membrane less than one-thousandth of an inch thick can be produced by this technique.

Since our last report, the same group of scientists have developed a new composite membrane which under final laboratory conditions has proven to be functional for increasingly long periods with no change in blood platelets or white cells, and can be maintained without continued use of heparin, an anti-clotting factor, which is normally necessary and interjects a high risk factor to the patient.

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. Initial studies have been completed in man and results indicate that reduction in infarct size can be achieved by this means. Determination has been made of optimal dose and how long it needs to be administered to achieve this reduction.

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. This technique is now being applied to the diagnosis of heart defects in infants too fragile to be subjected to risky, invasive techniques, and it is a non-risk method for all infants needing diagnosis.

Studies now in progress indicate that ASH may become clinically manifest in infancy, may be a factor in suddent 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.

This exemplifies that the potential of echocardiography in cardiovascular diagnosis is only beginning to be realized. Continue clinical evaluation of echocardiography may result in widespread use of what appears to be an extremely powerful non-invasive tool for the diagnosis and evaluation of a variety of cardiovascular disorders.

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 correcting the alpha/beta chain imbalance responsible for the clinical problems of Cooley's anemia by more direct means than periodic red-cell replacement.

PROGRAM MANAGEMENT

	1976 Rev. President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Program Management.....	$2,400,000	$3,000,000	$2,600,000	-$400,000
(Positions).....	(70)	(75)	(70)	(-5)

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).

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.

The 1977 budget provides for five fewer positions than in 1976.

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)

1976		1977 Authorization	1977 Budget Estimate	
Pos.	Amount		Pos.	Amount
---	$214,538,000	1/	---	$195,740,000

Purpose: This activity, administered by the Division of Heart and Vascular Diseases, includes 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--as well as detection, diagnosis, treatment and preventive programs. 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 rheumatic heart diseases, cardiomyopathy and infections of the heart, and circulatory assistance.

Explanation: 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 1976: Regression of arteriosclerosis has been conclusively demonstrated in non-human primates. Recruitment of the two largest arteriosclerosis clinical trials, the Multiple Risk Factor Intervention Trial and the Lipid Research Clinics has been completed. Over one million Americans were screened to obtain the 17,000 patients needed. Research in myocardial infarction continues to progress. Preliminary results in man offer the hope of reducing cardiac damage of a heart attack. New avenues of basic research concerning the early stages of atherosclerosis and the basic disease process of "sudden death" continue to be explored. There is convincing proof that many "sudden death" victims can be revived by prompt resuscitation. Hypertension research has focused upon causal factors for the development of the disease in young people, and the determination of why the Black population is stricken with hypertension at three times the rate of the non-Black population. The National High Blood Pressure Education Program appears to be succeeding since its inception three years ago since the number of patient visits are up by more than 40%, the number of unaware hypertensives has been halved, and the number of patients on effective therapy has been doubled from 4 million to 8 million. The hypertensive SCOR program continues, with competive renewals having taken place in 1976. The heart and vascular National Research and Demonstration Center, begun in 1975, has continued its functions of the optimal translation of the latest research advances into improved medical care.

Objectives for 1977: The major clinical trials--Multiple Risk Factor Intervention, Hypertension Detection and Follow-Up, Lipid Research Clinics, Coronary Artery Surgery, and Aspirin Myocardial Infarction Study will continue into more advanced stages of clinical data collection as patient screening and recruitment phases become completed. High priority will be given to programs in diabetes and cardiovascular sequelae; prevention, control, and education programs; the development of animal models of human disease; noninvasive instrumentation, and the protection of ischemic heart muscle. Important in 1977 will be the funding of a second round of arteriosclerosis Specialized Centers of Research.

1/ Authorization expired June 30, 1975. Extension legislation is pending.

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)

1976		1977 Authorization	1977 Budget Estimate	
Pos.	Amount		Pos.	Amount
---	$50,973,000	1/	---	$46,507,000

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 1976: Prime effort has been devoted, by design, to basic research; knowledge of the lung does not yet provide sufficient foundation to put great emphasis on the improvement of treatment. Research findings are laying the needed foundation for clinical advances of the future. Work has progressed at the cellular level which may have future impact upon hyaline membrane disease. A causative agent of hypersensitivity pneumonitis, a lung disease resulting from the inhalation of certain organic dusts, has been isolated and is now being used as a research tool to investigate the underlying mechanisms of the disease. Chemical extracts of cigarette smoke have been shown to adversely affect the ability of the cells responsible for clearing bacteria and debris from the lung to perform their functions. Other chemical extracts have been shown to induce fibrosis or scarring the lung. These studies add to the scientific basis for emphasizing the importance of smoking cessation programs. Current research in emphysema includes work on enzyme defects in the overall problem of chronic obstructive pulmonary disease, studies that may provide a basis for prevention of the disease. Important new work is ongoing at the pulmonary National Research and Demonstration Center, with special emphasis on occupational pulmonary disease resulting from prolonged exposure to harmful dust and fumes in various industries and occupations.

Objectives for 1977: The Institute will continue to support high priority programs in lung diseases. New findings, as for example, in basic cell physiology and in the role of enzymes will be further exploited. Important in 1977 will be funding of a second round of Pulmonary Specialized Centers of Research. These new or renewed Centers will address one of the four disease categories requiring further emphasis; namely, chronic diseases of airways, pediatric pulmonary diseases, fibrotic and immunologic pulmonary diseases, and pulmonary vascular diseases.

1/ Authorization expired June 30, 1975. Extension legislation is pending.

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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$57,102,000	1/	---	$52,100,000

Purpose: This activity, conducted by the Division of Blood Diseases and Resources, plans and directs research on blood diseases and blood resources. The program encompasses 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 1976. Work is progressing on the fundamental knowledge of hemophilia, where the development of alternate therapy is badly needed. Pioneering working is ongoing in the development of a cell-free system for protein synthesis enabling the study of human genetic defects in the test tube. Several leads are being pursued for the prevention of sickle cell disease. Most of these studies are in early phases, however, and clinically useful results are but distant possibilities. It has been found that low doses of heparin administered before surgery seem to prevent venous thrombosis and perhaps pulmonary embolism. The NHLI supports five Thrombosis Specialized Centers of Research. This program is being renewed in 1976. The National Research and Demonstration Center for blood resources continues with improvement of procedures for the acquisition, processing, storage, distribution, and clinical use of blood and blood products.

Objectives for 1977: High priority programs will include studies for more precise treatment of hemophiliacs, as well as antibodies which interfere with the efficacy of treatment; preventive programs in thrombosis, as well as pertinent clinical trials; basic research on blood diseases, including the sickle hemoglobin; the technology and management of blood resources; research aimed at reducing the hepatitis risk; and work on blood substitutes.

1/ Authorization expired June 30, 1975. Extension legislation is pending.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Intramural Research and Direct Operations. (Public Health Service Act, Section 301, Title IV, Part B, and Title XI).

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
672	$44,734,000	1/	634	$45,908,000

Purpose: This activity encompasses the basic and clinical research programs within the facilities of the NIH at Bethesda, as well as the majority of the administrative support staff of the Institute, including activities relating to review and award of grants, contracts, and reimbursements to NIH for centrally furnished services.

Explanation: The Institute's Intramural program is carried on in 13 major laboratories and branches. One hundred hospital beds are available to the clinical program at the NIH Clinical Center. Support is given to a vigorous out-patient clinical program with approximately 5,000 patient visits annually. Other direct operations include the costs of grant and contract review, award, and administration.

Accomplishments in 1976: Basic studies on lung cells maintained in tissue culture indicate that collagen molecules are produced and secreted by the various lung cells. In addition to producing collagen, studies show that lung cells also have lymphatic mechanisms to destroy excess or poorly formed collagen. 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; development of a new composite membrane, proven useable for increasingly long periods with no change in blood platelets or white cells, which can be maintained without continued use of heparin (which is normally necessary but interjects a high risk factor to the patient); practical clinical use of [illegible] alone or nitroglycerin plus phenylephrine in reducing ischemic heart-[illegible], arrhythmias, and other potential complications of acute heart attacks has been demonstrated as desirable. Initial studies in man indicate that reduction in infarct size can be achieved by this means; echocardiography can now provide non-risk diagnosis and evaluation of heart defects in infants; the disease entity known as Bartter's Syndrome (characterized by inability of patients to retain potassium) can now be controlled by application of prostaglandin synthtetase.

Objectives for 1977: Priority objectives include an intensive multifactor study of the clinical abnormalities of sickle cell anemia; clinical testing of the new composite membrane developed for the membrane oxygenator. On successful completion, study adaptation of membrane to other life support devices; further study of the sudden death syndrome in an effort to determine if preliminary findings indicating heart malfunction are correct; studies of the molecular basis of receptor function along with studies of short-term regulations of receptor activity. The major goal of these and related studies is a focus on the mechanisms which enable cells to communicate with one another and to respond to hormones and other external influences; continued studies of the causes of excessive connective tissue proliferation in fibrosis and interstitial lung diseases.

1/ Authorizing legislation expired June 30, 1975. Renewal legislation is pending.

National Institutes of Health

National Heart and Lung Institute

Program Purpose and Accomplishments

Activity: Program Management. (Public Health Service Act, Section 301, Title IV, Part B, and Title XI).

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
75	$3,000,000	1/	70	$2,600,000

Purpose: This activity provides the overall planning, direction, coordination, and evaluation of the Institute's programs. Included within this activity are: the Director and his immediate staff, including the Office of Administrative Management, the Office of Program Planning and Evaluation, and the Office of Prevention, Control, and Education.

Explanation: Funding for this area provides for salaries and other operating costs for overall Institute management. Activities include the establishment of internal Institute policy for program and administrative operations, and surveillance over their execution.

Accomplishments in 1976: In 1976 leadership was provided for continuing the implementation of the National Program plan, to "expand, intensify, and coordinate the activities of the Institute respecting heart, blood vessel, lung, and blood diseases..." This has encompassed an ordered sequence of program activities ranging from the acquisition of new knowledge to demonstration and control programs in the health care setting of the community. The emphasis on the whole continuum from basic research through clinical applications and health education has resulted in apparent significant reductions in the mortality from diseases within the Institute's purview.

Objectives for 1977: The Institute will continue the management and direction of its research programs. Emphasis will be placed on the coordination and evaluation of demonstration and control programs, including dissemination of health information. Programs primarily concerned with prevention will also be highlighted.

1/ Authorization expired June 30, 1975; extension legislation is pending.

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Estimate	Transition Quarter
1. Heart and vascular diseases..	$214,538,000	$32,800,000
2. Lung diseases.....	50,973,000	7,950,000
3. Blood diseases and resources.	57,102,000	8,950,000
4. Intramural research and direct operations.....	44,734,000	9,390,000
5. Program management.....	3,000,000	625,000
Total.....	370,347,000	59,715,000

Explanation

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 President's Budget. Estimates for individual programs were based on historical data for the first quarter modified by program impact of the FY 1976 estimate. No new programs or initiatives are planned during this period.

FRIDAY, FEBRUARY 27, 1976.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

WITNESSES

DR. JAMES B. SIDBURY, ACTING DIRECTOR AND SCIENTIFIC DIRECTOR OF THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT
DR. DONALD S. FREDRICKSON, 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 MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. We are still with the National Institutes of Health. This morning we have the National Institute of Child Health and Human Development.

The presentation is going to be made by Dr. James Sidbury, Jr. I see we have a biographical sketch of you, Doctor, which we will place in the record at this point.

[The biographical sketch follows:]

CURRICULUM VITAE, JAMES BUREN SIDBURY, JR., M.D.

Born: January 13, 1922, Wilmington, N.C.
College: Yale University, B.S., 1944.
Medical school: College of Physicians and Surgeons, Columbia University, 1947.
Marital status: Wife Alice, five children.
Intern: Medicine, Roosevelt Hospital, New York, N.Y., 1947–48.
Assistant resident: Medicine, Roosevelt Hospital, New York, N.Y., 1948–49.
Intern: Pediatrics, Johns Hopkins Hospital, Baltimore, Md., 1949–50.
Assistant resident: Pediatrics, University Hospitals, Cleveland, Ohio, 1950–51.
Assistant and instructor: Pediatrics, Emory University, Atlanta, Ga., 1951–53.
U.S.P.H.S.: Communicable Disease Center, Atlanta, Ga., 1951–53. Navy, V-12.
Private practice: Wilmington, N.C., 1953–54.
Attending physician: Babies Hospital, Wilmington, N.C., 1953–54.
Courtesy staff: James Walker Hospital, Wilmington, N.C., 1953–54.
Instructor: Pediatrics, Johns Hopkins University, Baltimore, Md., 1954–55.
Research fellow: Pediatrics, Johns Hopkins University, 1955–57.
Assistant professor: Pediatrics, Johns Hopkins University, 1957–61.
Associate professor: Pediatrics, Duke Medical Center, Durham, N.C., 1961–65.
Director: Clinical Research Unit, Duke Medical Center, 1961–___.
Professor: Pediatrics, Duke Medical Center, 1965–___.
Member: Mental Retardation Training and Research Study Section, 1972 to present.
Chief: Division of Pediatric Metabolism, Duke Hospital.
Staff: Lenox Baker Cerebral Palsy and Crippled Children's Hospital of North Carolina, Durham, 1974 to present.
Societies, memberships, etc.: Diplomate of National Board, 1948. Research Society of America, 1952. Licensed to practice medicine in North Carolina, 1953.

American Academy of Pediatrics, 1954– , New York Academy of Science, 1955–65, American Chemical Society, 1957–69, Society for Pediatric Research, 1957– , American Association for the Advancement of Science, 1958– , Maryland Heart Association, 1959–60. American Society of Human Genetics, 1959. Endocrine Society, 1961–64, American Pediatric Society, 1966– , Sigma Xi, 1967– , Southern Metabolic Club, 1969– . American Society for Pediatric Endocrinology, 1972– . Founder Member—The Lawson Wilkins Pediatric Endocrine Society, 1972– . Study section, NICHD, 1972– . Consultant, Watts Hospital, Durham, N.C. Board Director, N.C. Diabetes Association, 1971– . North Carolina Pediatric Society, 1963–75. Southern Society for Pediatric Research 1966– .

Honors and awards: Bicentennial Medallion (Pediatrics), Physicians and Surgeons, 1967.

Mr. FLOOD. Will you introduce your colleagues.

Dr. SIDBURY. Mr. Forbush is on the far right. Dr. Frederickson, you know. Dr. Corfman, director of our Center for Population Research, is next to him. On my left is Mr. Hedetniemi, our executive officer, beside him is Mr. Miller, our financial management officer. Behind me is Dr. Woodside, our deputy director.

Mr. FLOOD. We have here your prepared statement. How do you want to handle this?

Dr. SIDBURY. I would be prepared to read it if you wish.

Mr. FLOOD. Go right ahead.

Dr. Sidbury.

MISSION

The American people and the Congress have asked a great deal of the National Institute of Child Health and Human Development, that is, that we provide the research basis for producing a healthier population through preventive medicine for children. We believe that the best way to carry out this mandate is to insure the best possible start in life for every infant born in this country. If we can make every pregnancy a healthy and wanted pregnancy, if we can identify the causes of developmental impairments and understand the biological mechanisms involved, and if we can delineate the behavioral influences which act upon the developing child within the family and society, then we will be well on our way to guaranteeing each of our citizens a healthy childhood. All of our research is directed toward this end.

PROGRAM ORGANIZATION

The NICHD is composed of two major programs carried out through the Center for Research for Mothers and Children (CRMC), the Center for Population Research (CPR), and the intramural research program.

The problems addressed by the CRMC are those encountered in pregnancy, the birth process, infancy, and early childhood development. Areas of particular interest include prematurity, intrauterine growth retardation, the sudden infant death syndrome and other causes of infant mortality, and mental retardation.

The Center for Population Research supports studies intended to help in the formulation of population policies and to enable men and

women safely and conveniently to control their fertility and free themselves from reproductive impairments. In this effort emphasis is given to the biological, behavioral, and social aspects of the basic reproductive processes, to family planning and the regulation of fertility and infertility, including contraceptive development and evaluation; and to the causes of population change and its effects on the economic, environmental, and social aspects of the quality of life.

The intramural program of the NICHD is the internal research effort conducted in Bethesda, Md. The program combines biomedical research, behavioral research, and clinical studies. For instance, the Reproduction Research Branch is internationally known for its studies of sex hormones, and the Pregnancy Research Branch has developed one of the most useful animal models for studying pregnancy in a diabetic mother. Our newest intramural project is the Perinatal Center, where we have just opened a special care nursery to provide care for. and conduct clinical investigations of, high-risk infants. This nursery is NIH's first special care nursery, and the first inpatient service of the NIH devoted exclusively to the needs of infants. A program for the care and study of low birthweight, high-risk infants has been initiated primarily to evaluate those requiring chronic support and diagnostic studies. A number of disorders to be studied in this unit are antecedents of mental retardation.

RESEARCH PROGRAMS AND ACCOMPLISHMENTS

Now I'd like to review our research programs and accomplishments of the past year.

The steadily rising rate of unplanned pregnancy among teenage girls is a major concern, not only because of the burden which pregnancy imposes on the girls themselves, but also because the age of the mother is a critical factor in determining an infant's chances of survival. Low birthweight infants are particularly vulnerable to life-threatening illness, and one in every four of them is the child of a teenage mother. The United States has one of the highest rates of teenage pregnancy in the world, with 125,000 births occurring annually to mothers in their teens, nearly 60 percent of them to unwed mothers.

Other studies in human fertility are centered around the development of safer, more acceptable, and more effective means of fertility regulation. In addition to studies of chemical regulation, we are exploring the reliability and utility of other "natural" family planning methods. A contract has just been signed with Cedars-Sinai Medical Center in Los Angeles to evaluate the efficacy of a "natural" method based on recognition of changes in the character and quantity of cervical mucus during the normal menstrual cycle. These changes will enable a woman to determine when she is in the fertile phase of her cycle. The method will also help infertile couples to maximize their chances of achieving conception.

A major advance in preventive medicine occurred in October 1975, when NICHD released the results of its National Registry for Amnio-

centesis. Although tapping of amniotic fluid had been used as a prenatal diagnostic technique for a number of years, a number of obstetricians were concerned about possible unknown risks associated with the procedure. The study determined that amniocentesis performed in the middle 3 months of pregnancy is a safe technique, applicable to large segments of the population. Over 200 disorders based on chromosomal aberrations of inborn errors of metabolism can be diagnosed in utero using amniocentesis. The physician is now in a position to assure many parents-at-risk that they are capable of producing healthy children, thereby alleviating a major source of parental anxiety.

In addition to the disorders detectable by amnicentesis, there exist a myriad of structural malformations which have their origin in fetal development and may persist to handicap the victim for the duration of his or her adult life. The well-known "thalidomide babies," along with thousands of victims of the 1964 rubella epidemic, provide classic examples of such defects. But in most instances of congenital malformations, the causative factors, whether genetic or environmental, remain completely unknown. If we are to determine the underlying causes and mechanisms of these defects, we cannot limit ourselves to studying handicapped children. We must develop animal models which will permit us to experiment directly on the fetus during the time when the various organ systems are being formed. The NICHD is supporting research efforts in Atlanta, Portland, Seattle, and elsewhere in an attempt to develop such models.

Elimination of birth defects would certainly go a long way toward guaranteeing every child a healthy start in life. But there are further health hazards which may endanger even the well-endowed, well-formed fetus. These include intrauterine growth retardation, premature birth, and even the birth process itself. We are currently funding a number of studies to determine the exact effect of maternal malnutrition on the birthweight and subsequent development of the child. The studies have shown that children whose mothers received adequate protein and calories during pregnancy weighed more at birth and developed more rapidly than children whose mothers were malnourished.

Low birthweight infants are the major contributors to the unacceptably high infant mortality rate in the United States. Each year 240,000 infants are born too soon or too small for their gestational age. They are ill-equipped to face the challenge of life outside the womb, and approximately 45,000 of them will die in the first month of life. An even larger number will sustain lifelong disabilities. Since these infants can be identified as heavy contributors to a disabled population, NICHD has undertaken a significant effort to determine the mechanisms responsible for the premature onset of labor and to identify the causes of intrauterine growth retardation. Major studies are now underway in Dallas, Palo Alto, New York, and Boston.

If we could insure that all newborns were free of defects and mature enough to cope with the hazards of the first month of life, we would

automatically eliminate much of the infant mortality and morbidity in this country. However, there are certain additional dangers which may jeopardize the life of even the well-born infant. NICHD is particularly interested in two of these problems—maternal deprivation and the sudden infant death syndrome.

Maternal deprivation is a term used by behavioral scientists to refer to deficiencies in the immediate human environment which surrounds the infant. All infants need to be cuddled, played with, and otherwise stimulated in order to develop normally. When this stimulation is lacking, the result may be impaired development or, in the most extreme cases, early death. NICHD has been conducting a number of studies in this area. One group of researchers has shown that interaction between parents and their newborn infants actually improves the health status of the infants, in addition to enhancing the emotional security of the parents. These results are of particular relevance to the care of premature infants, who are often kept in virtual isolation for the first few weeks or months of their lives. We now realize that we have to make sure that these infants receive adequate stimulation in addition to good medical care.

We are also committed to saving the thousands of infants who survive the hazards of the first few months of life, only to fall prey to the sudden infant death syndrome. The sudden infant death syndrome, or SIDS, is the leading killer of infants in the postneonatal period, claiming more than 7,500 victims annually.

NICHD has assumed the primary Federal responsibility for the investigation of SIDS, and now has over 100 research efforts in progress around the Nation. These studies have radically altered the traditional picture of SIDS as a mysterious ailment which strikes a healthy infant without warning. We are now convinced that there is no single mechanism involved in SIDS. Nor were all of the SIDS victims as healthy as they appeared to be in the months preceding their death. Many of them suffered from subtle defects of a neurological, cardiorespiratory, and metabolic nature. We are rapidly approaching the time when we will be able to use these signs to identify the infants most at risk for SIDS, and, by appropriate treatment and special breathing monitors, prevent many of these deaths. In addition, these advances should help the parents of past SIDS victims to overcome their guilt feelings and their anxiety about the fate of future children.

For every family which loses a child in infancy, there are others who must face the ongoing tragedy of mental retardation, one of the most complex and critical problems of human development. NICHD has an enormous investment in this area. Investigations into the prevention and treatment of mental retardation are carried out in more than 200 projects directly supported by NICHD and in 12 mental retardation research centers around the United States. In the past year researchers at Yeshiva and Harvard Universities have identified certain basic steps in the maturation of the nervous system which must precede normal

intellectual and behavioral development. Investigators at UCLA, the University of Washington, the University of Wisconsin, and the University of North Carolina have achieved promising results in habilitation of the mentally retarded using behavioral adaptation techniques.

The foregoing discussion should demonstrate that the NICHD is compelled to examine all of the things which can go wrong between the decision to conceive and the emergence of the child as a self-sustaining individual. We have attempted to focus our research efforts in areas which offer promise of eliminating the major hazards of early life. We already know which risk factors pose the greatest threat to the infant: To be born too soon, or too small; to be born into poverty, or to a diseased or malnourished mother; to be born to a mother who is still in her teens or over 40; and to be born unwanted.

In order to minimize these risk factors and lower the national infant mortality rate, we must not only seek new knowledge, but find more efficient ways of applying it. We believe that this can best be accomplished by means of interdisciplinary research efforts involving both scientists and clinicians.

Toward this end, the NICHD will establish, through its Center for Research for Mothers and Children, a national network of research centers devoted to the study of diseases and disorders of pregnancy, infancy, and early childhood. These major research programs will be distributed around the Nation. Each will be devoted to a particular problem of maternal and child health, and each will allow researchers and clinicians to be brought together in a situation which will foster maximum exchange of information. For instance, a major research program devoted to the problem of prematurity would enable biomedical scientists and obstetricians studying the birth process to work side by side with pediatricians studying the premature infant. Research advances could be translated immediately into improved care for high-risk patients. Thus each major research program would serve as both a nucleus for research and a stimulus for higher quality medical care. Investment in child health is by far the best form of adult health insurance.

Mr. Chairman, the 1977 budget request for the National Institute of Child Health and Human Development is $129,883,000. I would be delighted to respond to any questions that you would like to ask 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 BUDGET REDUCTION

Mr. FLOOD. Dr. Sidbury, this budget proposes a reduction of $6,690,000 for your Institute in 1977.

Dr. SIDBURY. Yes, sir.

Mr. FLOOD. What is the impact of this proposed reduction? Are you going to reduce research on mothers and children?

Dr. SIDBURY. Our approach will be to spread the reduction across the programs of the Institute. We will have to tighten up the criteria and the budgets for those projects that we do fund. Most of this reduction will come in the grants area. It will reduce what we can accomplish.

Mr. FLOOD. Well, the impact is across the board then, right?

Dr. SIDBURY. Yes, sir.

Mr. FLOOD. Especially cutting on grants?

Dr. SIDBURY. Yes, sir.

CONTRACEPTIVE METHODS

Mr. FLOOD. In your budget justification you indicate you are going to be clinically testing new contraceptive methods. Will you elaborate on this breakthrough if that is what it is, that you have made on the development of new contraceptive methods?

Dr. SIDBURY. I think Dr. Corfman is the guiding light in that area and he could answer that very authoritatively.

Dr. CORFMAN. One project we are particularly pleased to start this year was referred to in Dr. Sidbury's statement. That is the clinical trial in the United States of a new form of natural family planning, or rhythm. It is a relatively new approach and has been enthusiastically endorsed by some advocates. It is our goal to test this method to see if it really works. That is one new effort we are undertaking now.

Another new project is one to develope a better injectible contraceptive for women. The work is now underway.

Mr. FLOOD. Of course, now you know there are many women in this country who do not wish to use or may not be able to use these contraceptive drugs and devices. How much of your research effort are you directing to the development of new contraceptive methods that are not dependent upon drugs or devices?

Dr. CORFMAN. The one large project is the one I already referred to. That is the project in Los Angeles to evaluate a new form of rhythm. We believe that the method will prove attractive to a large number of couples, not just Catholics, but other Americans who simply don't wish to use drugs and devices.

Mr. FLOOD. I said breakthroughs, not breakthrough. Is that the end of it?

Dr. CORFMAN. I am not sure I understand the question.

Mr. FLOOD. I asked it in two different ways, maybe that is why. What breakthroughs do you have in the development of new contraceptive devices?

Dr. CORFMAN. Excuse me, I thought you were limiting me to the discussion of natural family planning. If you are not, I can describe other projects. The third project is the clinical trial of an injectible contraceptive for men. We believe that men need modern contraceptives just as much as women. Those are three examples of new things we are

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undertaking this year. I will be glad to provide more information if you would like.

Mr. FLOOD. Yes.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

FURTHER COMMENTS ON CONTRACEPTIVE DEVELOPMENT

The contraceptive development program has continued to consolidate its priorities in the applied fields of drug synthesis and testing, exploration of new appraoches to fertility regulation, development of new testing systems for drug evaluation, and the support of directed biomedical research in specified areas. The approach has emphasized the search for entirely new drugs as well as looking at the contraceptive potential of existing drugs that are already approved for human use. The fact that contraceptive drugs are used on a chronic basis requires exhaustive safety studies in a variety of animal models, making the process of drug development both lengthy and costly.

The plan during the past fiscal year called for the concentration of human and fiscal resources on those projects having the greatest potential for improved contraceptive technology. A periodic and systematic review of ongoing projects has helped identify critical areas in the process of drug and device developments resulting in improved program performance. Limitations in both manpower and funding preclude the pursuit of a number of leads and necessitate hard management decisions to reach the goals stated in the 5-year plan. The synthesis program, therefore, is restricted to the development of relatively simple chemicals and avoids the isolation and purification of substances from natural sources. The size of our primate colony dictates that only drugs which have undergone exhaustive testing in other species will be evaluated in primates. Our ability to pursue esoteric leads in the ovulation detection area is also limited. The following sections describe some of the important developments in those research areas which were selected for emphasis during fiscal year 1975.

1. Drug development

Drug synthesis program.—The drug synthesis program has identified several potentially useful compounds which have undergone preliminary screening in animals. The precise mode of action of these new chemicals is still unclear but they have shown contraceptive activity in female laboratory animals. More extensive testing is awaiting synthesis of larger quantities of these chemicals. Their effectiveness cannot presently be ascribed to their known endocrine activities.

Several estrogens that were previously identified for continued exploration have undergone preliminary assessment in nonhuman primates. Available data suggest that their antifertility activity may not be greater than that of presently available drugs. These results point to the high risk inherent in the development of new contraceptive drugs. Work with these compounds in the coming year will confirm or refute their superiority over existing products.

The inhibitors of luteinizing hormone releasing factor (LRF—the biological substance which causes ovulation) have been shown to block ovulation in both rats and hamsters. New modifications have improved both the potency and duration of action of these compounds. Plans are in progress to evaluate their activity in nonhuman primates. This field of LRF inhibitors continues to be one of the more promising areas of our synthesis program.

Another promising lead involves the isolation and synthesis of a new compound which has been shown to block ovulation in hamsters. This simple compound was originally isolated from blastocysts (fertilized eggs). Its structure has been identified and quantities of it have already been synthesized. Studies are being conducted by several laboratories to determine its full sphere of ac-

tivity. This advance is a good example of cooperation between scientists involved in basic and applied research.

Drug synthesis facility.—Until recently a major bottleneck in the evaluation of new chemicals has been their availability. Invariably, the initial synthesis involves the production of only small quantities of these substances. Our expanded synthesis facility will have the capacity to provide larger quantities of compounds that have been identified as potentially useful. Present plans call for rapid synthesis of several compounds and a sufficient backlog of structures exists to keep this facility operating at peak efficiency. Its full potential should be clearly apparent during fiscal year 1976.

Biological drug testing facilities.—The biological testing facilities have continued to provide the contracpetive development program with rapid preliminary and in-depth evaluation of new drug. Operational changes have resulted in more rapid assessment of drug activities. This increased efficiency should prove useful in two essential ways: (1) shorten the time of decisionmaking and (2) result in savings of funds.

Male contraception.—The new clinical trials of male contraceptives were not implemented in fiscal year 1975 because regulatory requirements could not be completed as originally scheduled. All the preliminary requirements have now been satisfied and these trials began during the early part of fiscal year 1976. They should help decide whether the administration of synthetic male hormones is a reasonable approach to male contraception.

New approaches to male contraception are presently being tested in monkeys. These animals may prove to be a good model for ascertaining biological activities in humans.

2. Device and systems development

Drug delivery systems.—The study of new biodegradable drug delivery systems has reached the stage of comprehensive evaluation in different animal models. Advances have been made in microencapsulation of drugs which in turn permits the use of syringes for administration, and should improve their acceptability. The animal studies that have been completed suggest that a steady release of a drug can be accomplished, but considerable amount of research is still required before human experimentation can be instituted.

The proper understanding of these drug delivery systems has the potential of improving not only contraceptive methodology but also therapeutic techniques in other areas of medicine as well. The next two years should provide us with crucial evidence in this complex research area.

Long-acting injectable contraceptive.—During fiscal year 1975, the NICHD negotiated a contract to provide for research required to bring a long-acting injectable contraceptive for women to the U.S. marketplace. The initial 3-year contract calls for studies in both animals and humans which are required by FDA regulations. This drug is presently being tested on a much wider scale in other countries and the results obtained in those trials will guide the Institute in making future decisions.

Devices.—The fluid-filled IUD has been tested in 300 women volunteers. Although the preliminary results were encouraging as the number of IUD insertions increased, it became apparent that the expulsion rate for these devices was high and consequently was of limited utility. The women who did not expel the device are being followed for an additional year, but no new insertions are being made.

The instrument (steerable hysteroscope) used for viewing the uterine cavity and identifying openings of the fallopian tubes has been used successfully in women undergoing procedures such as D & C (dilatation and curettage), hysterectomy or laparoscopy for benign diseases. It therefore appears that the utility of this instrument for viewing the uterine cavity and openings of the oviducts has been successfully demonstrated. Plans have also been implemented to compare the steerable hysteroscope to commercially available regid instruments in order to ascertain its advantages or disadvantages.

The development of devices for occluding the tubal openings and thus rendering the patient infertile has been slow. It is doubtful whether rigid or semirigid plugs

can be safely insterted in human fallopian tubes. The nonsurgical occlusion of fallopian tubes has been a universal problem and new approaches are being implemented to solve it. During the next fiscal year both the utility of the hysteroscope and the value of the new tubal occlusive systems should be ascertained.

3. Noncontraceptive fertility regulation

Natural family planning.—During fiscal year 1975, plans were completed to sponsor research to determine the efficacy of the Billings' method (cervical mucus technique) of natural family planning. This method of fertility regulation is dependent on teaching women to perceive their reproductive status as revealed by the nature and extent of cervical mucus secretion. Prior to ovulation and for several days thereafter the mucus is copious, fluid and lubricating, and it is at this time that coitus should be avoided. In view of the fact that the method is not dependent on drugs or devices, it has special appeal to certain segments of the population.

Ovulation detection.—Fertility regulation can be accomplished by the avoidance of coitus about the time of ovulation. However, there are no practical methods which can predict or pinpoint the time of ovulation in women. Availability of a reliable, simple and inexpensive method of ovulation prediction would permit the woman to identify the safe and unsafe period of her cycle. The Institute has funded several projects to develop such methods. This program may be expanded in fiscal year 1976 to incorporate additional projects.

4. Directed fundamental research

As was mentioned previously, there has been a reduction in contract support of fundamental research. Nevertheless, even with reduced support, important advances have been achieved in several areas.

Cervical physiology.—The cervix serves as a barrier between the uterus and the vagina and can either facilitate or impede the transport of sperm. To a very large degree it is the fluid (mucus) secreted by the cervical glands that serves as the controlling factor in sperm transport and survival. Research on the cervix of the human and the nonhuman primate indicates that this organ has steroid hormone receptors similar to the uterus and that these receptors most likely control cervical function. Alteration of the circulating levels of estrogen and progesterone (hormones) change the quantities of these receptors and influence the composition of mucus. Direct research on the mucus during various stages of the menstrual cycle is helping to identify the biochemical components responsible for its viscous or fluid properties, characteristics which appear to have a direct bearing on fertility.

Pregnancy determination.—In the overall scheme of contraceptive drug development the nonhuman primate serves as a final model for the indication of human utility. Since the presence or absence of pregnancy is the definitive endpoint of a drug's activity, it is critical that pregnancy be diagnosed accurately at the earliest possible stage. Collaboration between NICHD scientists and researchers at other institutions has resulted in the development of a reliable and simple test kit. The Center furnishes these test kits to scientists all over the world.

Mr. FLOOD. In your justification you state ongoing projects will continue to explore a relationship between various contraceptive methods and birth defects among the offsprings of users of various contraceptive devices?

Dr. SIDBURY. Yes, sir.

Mr. FLOOD. What progress have you made in this area? What have you learned?

Dr. SIDBURY. Research supported by the Center for Population Research has shown an increased incidence of congenital heart and limb abnormalities in infants born of mothers who have taken the

pill during the first 3 months of pregnancy, not knowing they were pregnant.

Looking into this further, researchers have also shown that these mothers have a decreased level of pyridoxine, one of the B vitamins, and a decreased level of folic acid and zinc. Zinc and pyridoxine are known from experimental models to be associated with the induction of congenital anomalies. If it is determined that the decrease of either the vitamins or zinc is related, prevention will be easily accomplished.

Mr. FLOOD. In the past couple of years the number of vasectomies that have been performed have increased substantially.

Dr. SIDBURY. Yes, sir.

Mr. FLOOD. Are you doing any work to determine the adverse effects, if any, on this kind of operation? Tell us what kind of side effects you have identified to date.

Dr. SIDBURY. From a scientific standpoint the side effect we have identified is a very fascinating one. From a human standpoint it is a little frightening. The studies have shown that there is a certain low percentage of normal males who have circulating antibodies in their blood to the sperm. If you do a vascetomy and look at that same group after 4 months, there is a new antibody to sperm that is involved. Look at them 12 months later and the frequency goes up to about 30 percent or greater who have this new antibody to sperm.

This work has proceeded in a very sophisticated way to the point where researchers can show that the second antibody produced is to the DNA protein in the sperm. This finding has implications which the Center for Population Research is now in the process of trying to identify and to determine the ramifications. Potentially, it is quite significant.

Mr. FLOOD. What have you and your scientists learned about the association of the pill with heart attacks among women who use the pill?

Dr. SIDBURY. The incidence of high blood pressure, induced abnormalities in glucose tolerance, the enhancement of blood clotting are, in fact, complications that certainly enhance the risk of coronary artery disease. Is this a genetic response? In other words, is this going to happen in everyone? The answer is certainly not. This suggests that there is a genetic predisposition to respond in this way.

Mr. FLOOD. Do you routinely notify the Food and Drug Administration people about any of these adverse effects that you discover about a particular contraceptive drug or device?

Dr. SIDBURY. Yes, sir. Dr. Corfman has worked on a continuing basis with the Food and Drug Administration people in this context. It has been a functional type of interrelationship. We are very concerned about this.

Mr. FLOOD. Have you notified them of any adverse effects of a particular contraceptive drug or device within the last year?

Dr. SIDBURY. Let me have Dr. Corfman respond to that.

Dr. CORFMAN. Yes, within the last year we have been able to notify them of the results of our studies on the relationship between oral contraceptives and breast cancer. Fortunately, both of those studies indicated a negative relationship.

We also have told them of the relationship between pills and nutrition, especially vitamins.

Another thing we have been able to do is to confirm the fact that the less the amount of estrogen in the pill, the less apt a woman is to get thromboembolism. As a result, the amount of estrogen in pills has been reduced and this, in turn, has resulted in a decrease in deaths from thromboembolism.

There are other examples in relation to intrauterine devices and vasectomy.

Mr. FLOOD. What action has the FDA taken as a result of your motivation?

Dr. CORFMAN. One specific action is the recommendation that the amount of estrogen in pills be reduced.

EFFECTS OF FAMILY SIZE

Mr. FLOOD. Doctor, you mentioned in your justification that research concerning intelligence of offspring and family sizes shows an inverse correlation of some kind. Can you tell us more about this research? How was it conducted?

Dr. SIDBURY. This is a matter of looking at the performance; how well the children do both healthwise and schoolwise, IQ performance, and motivation as a function of the size of the family.

Mr. FLOOD. How is that done?

Dr. SIDBURY. By taking a population group and identifying within the group the families with various numbers of children; separating these, and categorizing how each did over a period of time in relation to the school performance, their job attainment, and other factors.

It is a retrospective type of approach.

INFANT MORTALITY RATE

Mr. FLOOD. You said on page 50 of your justifications that the infant mortality rate now stands at 17.6 deaths per thousand births. Now, just a few days ago. Dr. Theodore Cooper was here and told us the infant mortality rate was 16.2 per thousand births. Did something happen in the last few days we should know about?

Dr. SIDBURY. The figure Dr. Cooper gave you is a provisional rate for 1974 which is a more recently projected rate.

Mr. FLOOD. We certainly hope the other data in the justifications is more accurate. Now what about it?

Dr. SIDBURY. The 16.3 figure that Dr. Cooper gave is an update and more recent estimation of what the most recent figure will be.

Mr. FLOOD. Which is it? Where are we? Which one is it? Are you talking about the same things or what?

Dr. SIDBURY. The figure we use is from a year earlier, 1973. The important thing is that we are seeing a continual decline in the infant mortality due to the medical practices and procedures which have been stimulated.

SUDDEN INFANT DEATH SYNDROME

Mr. FLOOD. How much are you going to spend in this proposed 1977 budget for research on the sudden infant death syndrome? How does that compare, whatever you are going to spend, with what you spent in 1976?

Dr. SIDBURY. $6.4 million approximately for fiscal 1977 compared to $6.8 million in 1976.

Mr. FLOOD. What new developments have come about in this area as far as prevention is concerned?

Dr. SIDBURY. There have been some very exciting developments in this area which one would have thought would not lend itself at all to research. What has become very clear is that the sudden infant death syndrome is a composite of a number of different diseases or physiological abnormalities. For example, it has been shown that the enzymes having to do with glucose formation in one group of infants is markedly decreased. There is evidence from the pathology in the lungs of the infants who have died that there is a thickening of an arterial muscle which indicates they have been under low oxygen stress for a period of time. It is not just a sudden thing.

So it is something that has been ongoing. Further, the behavioralists have shown that the breathing pattern of these infants can, in fact, predict who is at risk. There is a tendency of these children to have longer periods of not breathing. A normal infant will breathe a while, have a bit of a rest and pick up again. These children have a tendency to have more trouble starting up again.

There is evidence in another group of an immunological defect. There is evidence in another group and even an animal model can be produced, where the animal tends to overreact, if you will, to milk and to glucose but not to salt water, causing a constriction of the windpipe. Then there is another group where researchers have demonstrated, in fact, an abnormal rhythm of the heart, wherein the heart doesn't beat in the normal fashion.

The provocative part of that is that scientists have also shown that the parents, one or both, may have an abnormality in their EKG as well, suggesting a genetic basis.

Mr. FLOOD. Your Institute conducted several planning workshops back in 1975 concerning the sudden infant death syndrome. How effective were they?

Dr. SIDBURY. I would recommend this as a model, as a matter of fact, when you are up against a problem without clear leads. This is

unquestionably the mechanism that got the ball rolling in SIDS because there was nobody working in the area at the time the mission was given to us.

By getting these people together who were working in potentially related areas and having them focus on the problem, they were stimulated to accrue pertinent data in a relatively short period of time. I think they have made very impressive progress. So it has really paid off.

DIABETES RESEARCH

Mr. FLOOD. You also mentioned the problem of low-birth-weight babies. How many of those children were born to diabetic mothers—most of them?

Dr. SIDBURY. No, sir. Diabetic mothers tend to have big babies. You tend to deliver these babies early to avoid some of the problems of diabetic babies. If the diabetes is poorly controlled the infants may be born prematurely.

Mr. FLOOD. What kind of research are you supporting regarding diabetics?

Dr. SIDBURY. Two basic studies. Our purview in the area of diabetes is the mother with diabetes and the infant of the mother with diabetes. These are the areas we have addressed. In the intramural program we have an animal model for studying just this question.

MENTAL RETARDATION

Mr. FLOOD. Will the 1977 budget request permit you to support the 12 mental retardation research centers at the current rate of support?

Dr. SIDBURY. It is the plan to continue the core support of those centers at the same rate, yes, sir.

Mr. FLOOD. In your justification you mention an automated system that may be useful for screening children for genetic defects which may have a bearing on mental retardation. Can you tell us a little more about this?

Dr. SIDBURY. I agree with your interpretation 100 percent. I think this will potentially have a tremendous impact and bring a great deal of meaning to the amniocentesis program. The problem with cytogenetics is that it is such a tedious thing. If you want to make an impact you should make it available to a large number of women. The man-years this will require in terms of chromosomal analysis is astronomic. If this automated technique will work, it will have a tremendous impact in making possible the chromosomal analysis for a large number of people in prenatal diagnosis.

Mr. FLOOD. What significant contribution has behavior modification techniques produced in the treatment of the mentally retarded? Suppose you describe for the committee the behavior modification techniques you are supporting.

Dr. SIDBURY. Basically these are simple techniques where you want to develop a specific type of response on the part of the child. This is particularly useful in a mentally retarded child where communication is difficult but you want to teach him to eat with a spoon or fork, to dress himself; the simple things that will make a difference in his care.

By a system of ongoing rewards you can develop this type of behavior in a relatively short period of time. The techniques have been very useful.

EPIDEMIOLOGY OF INFANT MORTALITY

Mr. FLOOD. Looking at page 64 of your budget justifications, you state that your research program will link infant birth and death certificates for several States. Are you going to conduct this project in conjunction with the National Center for Health Statistics or are you going to do that independently?

Dr. SIDBURY. This project will be conducted by epidemiology and biometry staff and they will coordinate their efforts.

Mr. FLOOD. If it is not done in conjunction with the National Center for Health Statistics, why not?

Dr. SIDBURY. It will be. It has to be. That is where the data is obtained. Our effort will be in the interpretive aspect rather than the actual data collection.

Mr. FLOOD. They routinely collect these statistics?

Dr. SIDBURY. Yes, sir. It will be their data that will be used.

Mr. FLOOD. Thank you.

Mr. Michel?

Mr. MICHEL. Thank you, Mr. Chairman.

COORDINATION WITH HEALTH SERVICES ADMINISTRATION

Dr. Sidbury, in reviewing Dr. Kretchmer's statement, it appears many of your activities overlap and parallel the activity of the Health Services Administration. What kind of communication do you have with that agency to coordinate your activity and prevent any duplication?

Dr. SIDBURY. We have several formal mechanisms but I think what really counts is that we have very good personal relationships and interactions with them. It is really a functional interaction.

Mr. MICHEL. Do you think both sides are conscious of the fact that there is no need to be duplicating things?

Dr. SIDBURY. Yes, sir.

Mr. MICHEL. Now, the maternal and child health program in the Health Services Administration has research grants and you have research grants in the area?

Dr. SIDBURY. Yes, sir, there is a difference in thrust.

Mr. MICHEL. Can you tell me a little about that?

Dr. SIDBURY. Ours is a basic research type of orientation, if you

will. Theirs is research on how to deliver health care, how to deliver it best and get the results that we obtain to the people, to the child.

CAUSES OF POPULATION CHANGE

Mr. MICHEL. Now in the statement your shop indicates that the center for population research is studying, among other things. "The causes of population change and its effects on the economic, environmental, and social aspects of the quality of life." That is a big mouthful. Isn't this getting rather far afield from medical research?

Dr. SIDBURY. Not really. What we are doing is fine tuning our approach in the area of contraception and population control. One of the big hangups in terms of the delivery of the product, if you will, is why don't the people who really need the help, the contraceptive information we provide, why don't they avail themselves? What is there about the black box that they reject? That is basically the question we are addressing. What are the factors we are not cognizant of that would improve the end result?

Mr. MICHEL. How much money in this budget to which you are testifying would go for this aspect of your work?

Dr. SIDBURY. I think Dr. Corfman has that figure.

Dr. CORFMAN. The amount of funds that we would allocate to social science research for 1977 will be about $8.1 million.

Mr. MICHEL. What is that compared to 1976?

Dr. CORFMAN. Almost the same, $8.5 million.

Mr. MICHEL. I was inclined to think from looking over some of this that when you get into this economic social thing, you get in the realm of politics but I suspect in the final analysis it is probably a pretty difficult thing to separate going to the heart of your last response there, if it is a question of family planning. That is kind of a delicate line to walk.

Dr. SIDBURY. Yes, sir.

Mr. MICHEL. Do you really have any guidelines or limitations placed on this research?

Dr. CORFMAN. You are touching on a very difficult topic, that is, to define how far afield we should go in the social sciences. We have a rule that we will not accept applications unless they are relevant to health, whether it be the health of families, children, or society. We reject applications which are obviously not within our mandate.

Mr. MICHEL. Is your shop the one which awarded the grant for the study of love about which Senator Proxmire was all exercised here recently?

Mr. FORBUSH. That was the National Science Foundation.

INTRAMURAL BEHAVIORAL RESEARCH

Mr. MICHEL. What is the nature of this behavioral research which you are conducting as part of your intramural program?

Dr. SIDBURY. This, simply put, is a behavioral study of mother-child interaction.

Mr. MICHEL. What don't we know about that that we ought to know?

Dr. SIDBURY. Well, there are a number of things that have come out that are of interest. The reaction of the infant sets up the reaction in the mother. It is a two-way street.

Mr. MICHEL. Do we know yet which is worse, whether the child is more adversely affecting the mother or the mother more adversely affecting the child?

Dr. SIDBURY. It is an individual situation, but there are means of seeing how delicate the balance is. There are now methods to intervene to break up the vicious cycle when it gets underway. There are pragmatic results from the studies.

FETAL RESEARCH

Mr. MICHEL. Does any of your research in the family planning field use aborted fetuses?

Dr. SIDBURY. No, sir.

Mr. MICHEL. Now you say in your statement:

> We must develop animal models which will permit us to experiment directly on the fetus during the time when the various organ systems are being formed.

Is such research going to be limited strictly to animals or is it likely to involve humans?

Dr. SIDBURY. It is limited to animals. That is why the animal model is so important to us.

Mr. MICHEL. Dr. Fredrickson, since you are here, are any of the other institutes funding research which are using aborted fetuses in some way or another?

Dr. FREDRICKSON. I think the answer is that all are in conformity with existing laws and regulation but I cannot give you a categorical answer. I will answer that for the record.

[The information referred to follows:]

NIH INSTITUTES FUNDING RESEARCH USING ABORTED FETUSES

The National Institutes of Health has supported no research involving the living aborted human fetus since April 1973. At that time, the NIH identified two supported activities involving such research and instructed the responsible principal investigators to terminate any work on the living abortuses. Since then, no research of this type has been approved. No applications or proposals to conduct such research have been received within the last 2 years. During the period of the moratorium on fetal research imposed under section 213 of the National Research Act, only one inquiry concerning research on a live abortus was received and the investigator advised that the research would not be supported and should not be conducted.

Thus, NIH is not knowingly providing support for any research on living aborted human fetuses for which medical science can offer no hope for survival (the nonviable fetus). Before any such research would be permitted, a determination must be made in accordance with section 46.209, subpart B, part 46, title 45 of the Code of Federal Regulations that certain restrictive conditions are met. Section 46.209 reads:

Activities directed toward fetuses ex utero, including nonviable fetuses, as subjects.

(*a*) No fetus ex utero may be involved as a subject in an activity covered by this subpart until it has been ascertained whether the particular fetus is viable, unless: (1) There will be no added risk to the fetus resulting from the activity, and (2) the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(*b*) No viable fetus may be involved as a subject in an activity covered by this subpart unless: (1) Vital functions of the fetus will not be artifiically maintained except where the purpose of the activity is to develop new methods for enabling fetuses to survive to the point of viability, (2) experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and (3) the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

(*c*) In the event the fetus ex utero is found to be viable, it may be included as a part in the activity only to the extent permitted by and in accordance with the requirements of other subparts of this part.

(*d*) An activity permitted under paragraph (a) or (b) of this section may be conducted only if the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: (1) his identity or whereabouts cannot reasonably be ascertained, (2) he is not reasonably available, or (3) the pregnancy resulted from rape.

NIH does permit sound research on the viable fetus to improve the chances of survival of that fetus in particular and premature infants generally, including those with disorders or problems that may yield to such research efforts. The subjects of such research are considered infants at the time of birth, however, not fetuses. An aborted fetus estimated to be less than 20 weeks of gestational age and weighing less than 500 grams (one pound = approximately 450 grams) is usually considered nonviable.

The inquiry does not differentiate between live aborted fetuses, or whole, defective, or disintegrated dead fetuses. Therefore, we interpret it to include all of these possibilities.

NIH does support a number of research activities using materials, fluids and tissues derived from dead aborted fetuses. Such materials may be used, for example, for gross and microscopic examinations, and biochemical analysis for defects that may correlate with genetic, congenital, environmental or other known or suspect factors.

Human fetal tissue and cells are used for research on viruses of human origin or in a search for viruses that may cause cancer, arthritis and other human diseases whose cause is still unkown.

Before human tissue can be used from any source, including dead fetuses, review and approval by the Institutional Review Board in accordance with title II, Public Law 93-348, and the basic DHEW regulations on protecting the rights and welfare of human subjects must be certified. Assurances from grantee and contractor institutions also require adherence to state and local laws and the documentation of informed consent from parents. State laws generally conform to the National Anatomical Gift Act.

TEENAGE PREGNANCIES

Mr. MICHEL. When Dr. Cooper was here I asked how teenage pregnancies in our country compared with those in other nations. He said a comparison was difficult because of different data base. In your statement you indicate we have one of the highest rates. Is that really just kind of repeating Dr. Cooper's statement? I find that awfully hard to believe having traveled extensively in Africa, for example. Again, it must have to do with just the countries that have a good data base for statistics.

Dr. SIDBURY. I am sure you are right.

Mr. MICHEL. It is nothing we want to minimize but in proper perspective I think the record should show that, but by no means to minimize it.

Have you developed any conclusion as to why we have one of the highest rates, since it said so in the statement?

Dr. SIDBURY. I think the important point here is that the rate is increasing. Not only is the rate high, but it is increasing.

Mr. MICHEL. Now is it beyond your realm of expertise in research to tell me how we can begin to turn that around? Does that get into somebody else's bailiwick?

Dr. SIDBURY. Dr. Corfman is very concerned about this subject. I think he would like to field that question.

Dr. CORFMAN. As for the teenage pregnancy rate, we have one of the highest rates in the developed countries. I certainly agere that such rates are also very high in developing countries because in those countries children marry early and have their own children early. They also have many children. But as for Western countries, we have here one of the highest rates.

New Zealand's rate is high, too. They also have almost an epidemic of illegitimate and teenage pregnancies.

NIH cannot solve the American problem alone. It is a social and economic problem, but we certainly can deal with it.

One of the things we have done is to get the data so that we know we have a problem. We have analyzed these data so we know where we are with this problem and what we can do about it. We have also done motivation studies with teenagers. We know something about their contraceptive preferences and practices.

So public health agencies can adjust their family planning programs to the needs of teenagers. We certainly need better contraceptive methods. If young people are going to have sexual intercourse, they should have proper methods available.

Dr. FREDRICKSON. It is interesting also to point out that this increase is not limited to any single ethnic or economic group. It is widespread throughout the population.

Mr. MICHEL. I must confess sitting up here on this side of the table that I can't give you the answer and I don't know if you can altogether give us one either. I have a difficult time rationalizing in my own mind. One time you want to have public education about it. The more public education about it that you have in a sense gives indirect credence to engaging in a practiec which we know causes it all in the first place. I just don't know how.

Dr. CORFMAN. We don't know of any evidence that sex education in the schools has any effect on sex practices. We do know that juveniles are alarmingly ignorant about contraceptives.

Mr. MICHEL. By the same token we can't turn our back on it either. Those of you who are smarter than we are, I hope you come up with some answer in that regard. I guess it goes back to what kind of real values you end up getting taught in the home. That probably is the most important kind of teaching anybody can impart.

Dr. CORFMAN. Yes, sir.

PRENATAL CARE

Mr. MICHEL. I note your funding research shows that malnutrition on the part of the mother results in more poorly developed babies. That is something we have known for years. Is there anything extraor-

dinarily new about this we don't know? Isn't it mostly just a need for a public education program?

Dr. SIDBURY. Actual data regarding this point is relatively recent; prior information was based on impression. What we have come up with is that actually it is more impressive than we had thought, both from the standpoint of the mother's health and complications during pregnancy, and the effect on her offspring for years to come.

Study subjects have been followed up through school years. Their school performance is unquestionably different from those who were not affected.

Mr. MICHEL. How about smoking mothers during the period of pregnancy? Do we know enough about a smoking mother, if she resists the temptation to smoke during the period of pregnancy as distinguished from having done so before, does that make any difference?

Dr. SIDBURY. There is evidence that smoking is detrimental to the fetus but it is not that clear cut.

Mr. MICHEL. How about alcohol?

Dr. SIDBURY. Alcohol, no doubt about it. There is the fetal alcohol syndrome. You can reproduce that in animals. The child ends up with a form of mental retardation that is very significant.

Mr. MICHEL. Would you recommend total abstinence from alcohol during the period of pregnancy?

Dr. SIDBURY. The mothers we are talking about here are chronic alcoholics.

Mr. MICHEL. Are you saying that use in excess amounts or beyond moderation leads to trouble?

Dr. SIDBURY. This is a complicated problem because the chronic alcoholic has a number of nutritional deficiencies and other related health problems.

SUDDEN INFANT DEATH SYNDROME

Mr. MICHEL. The sudden infant death syndrome, the chairman asked specifically for the amount. Isn't there a slight reduction in the dollar figure of 1977 over 1976?

Dr. SIDBURY. Yes, sir.

Mr. MICHEL. I don't think you want to impart by that reduction in figures that we are not interested in getting to the heart of this particular problem.

Dr. SIDBURY. Thank you. I would certainly like to emphasize that.

Mr. MICHEL. Is there any way that we can buttress the record or buttress that comment by pulling off from other areas the difference between what we spent last year and this coming year? I think that would probably have to be shown. There is always that temptation. The problem is still with us. It is growing. Why do we cut back?

Dr. FREDERICKSON. Mr. Michel, if you would desire, we can prepare that information for the whole of NIH. This is the major Institute for supporting such research. Some of the research related to the SIDS problem was in the conduction defeat done by the intramural research progarm of the Heart Institute. We can compile it and project it for 1977 if you would find that useful.

Mr. MICHEL. All right.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT—OBLIGATIONS FOR PROGRAMS IN SUDDEN INFANT DEATH SYNDROME

	1976 estimate	1977 estimate
National Institute of Child Health and Human Development	$6,830,000	$6,400,000
National Institute of Neurological and Communicative Disorders and Stroke	35,000	----------
National Heart and Lung Institute	30,000	30,000
National Institute of Arthritis, Metabolism, and Digestive Diseases	35,000	35,000

Mr. MICHEL. Did I understand from your response to the chairman there, Doctor, that we already get some kind of reading that if there is an abnormality in either of the parents of that child, heartwise, the chances are that it could show up in that child?

Dr. SIDBURY. Yes, sir.

Mr. MICHEL. What is the other thing you made reference to?

Dr. SIDBURY. The respiratory abnormality that you can monitor.

Mr. MICHEL. An overreaction to milk?

Dr. SIDBURY. Yes, and to glucose causing the windpipe to go into spasm.

Mr. MICHEL. What would cause that?

Dr. SIDBURY. This is an abnormality of the reflexes. This is not a normal type of reflex response. So it fits in with the total picture of their nervous system not being either properly matured or integrated at that particular critical age between 2 and 6 months.

Mr. MICHEL. It used to be called crib death. When you least expected it, the reaction takes place and shuts off the windpipe or denies it oxygen.

Dr. SIDBURY. In one group which was studied, that would be the mechanism. It is very curious that the overwhelming majority of these events occur between 12 midnight and 8 in the morning.

Mr. MICHEL. Having done my trek years ago of that 10, 2, 4 routine up and down, do we know that the denial of that regular feeding affects the child—you know that is not the most comfortable chore to get up at 2 or 4 in the morning. Do we know about that yet?

Dr. SIDBURY. What is curious is that this is true for SIDS in general. The ones in regard to the milk response are a small segment. We are talking about different things but they all curiously follow the same pattern in terms of time.

Mr. MICHEL. So you think we are making some progress toward recognizing the problem?

Dr. SIDBURY. Yes. In fact I think we are at the point of reaping the harvest.

Thank you.

BUDGET REDUCTION FOR THE CENTER FOR RESEARCH FOR MOTHERS AND CHILDREN

Mr. NATCHER. Your budget specifically reduces the program for mothers and children by $5,036,000. Considering the fact that the United States ranks 15 in infant mortality, do you think this reduction is appropriate at this time?

Dr. SIDBURY. What we will do is to tighten up and get more for the buck. In the best of all worlds one could conceive of putting more funds into this field, but we are trying not to go too fast, so that the

centers we develop will be really productive ones. So we are not going to try to go too fast but to go with quality.

Mr. NATCHER. Doctor, what specific areas of maternal research would you have to discontinue as a result of this budget reduction? Can you give us any idea as to where you are going to have to make your changes?

Dr. SIDBURY. It is difficult to give you a specific answer because in the granting process we fund the applications that have the highest merit ranking. There will not be any specific deletions. It is across the board. We will continue to fund the projects that are of the highest quality and look like they have the greatest chance of payoff.

Mr. NATCHER. At this point in the record would you place a statement showing those you consider of the highest priority and importance and where the reduction will be made?

Dr. SIDBURY. Yes, sir.

Mr. NATCHER. Submit a short statement to be placed in the record at this point.

[The information follows:]

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

RESEARCH FOR MOTHERS AND CHILDREN

The primary area of reduction in the research for mothers and children program is in the grant component. The reduction of $1.3 million in the pregnancy and infancy activity will curtail research on infant morbidity and mortality, with particular impact on the development of the major research programs for mothers and infants; the sudden infant death syndrome; and the events surrounding the birth process. The reduction of $2.4 million in the growth and development area will reduce our research efforts on the role of nutrition in physiological and intellectual development; the learning process, especially the acquisition of language skills; and the problems of growth and physiological maturation. The reduction of $1.3 million will result in the cutback of our research effort in the prevention and amelioration of mental retardation with particular effect on the research in genetics and inborn errors of metabolism, the early diagnosis of mental retardation, and the social and environmental factors which contribute to intellectual deficiencies.

PYLORIC STENOSIS

Mr. NATCHER. I know of a case where a little boy 3 months of age, where that portion of the stomach that empties into the intestine closed and it required an operation. The surgeon who performed this operation said this happens with boy babies and never with girls or very seldom. Is that true?

Dr. SIDBURY. Yes.

Mr. NATCHER. Why is that?

Dr. SIDBURY. I believe you refer to a condition called pyloric stenosis. It is much more common in the male baby. It does fortunately respond to a simple operation and the results are excellent.

Mr. NATCHER. In this particular case the surgeon said that he had performed a number of these operations on male children, and never a female.

Dr. FREDERICKSON. That means the determining defect must be on the X chromosome.

Mr. NATCHER. It is a rather simple operation and very successful with no problems later?

Dr. SIDBURY. That is correct.
Mr. NATCHER. Thank you, Mr. Shriver?

MENTAL RETARDATION RESEARCH CENTERS

Mr. SHRIVER. Dr. Sidbury, in looking over your request, I am concerned that you appear to be cutting back on some ongoing research programs while you are initiating a number of new programs. This, together with the reduced budget request, could threaten some excellent programs. I refer specifically to the efforts of existing mental retardation centers, one of which is in Kansas City. What is the funding outlook for these centers? I would hope it would be sufficient for them to retain the fine staff they have been able to put together.

Dr. SIDBURY. I, too, share your concern about the Mental Retardation Research Centers. The 12 existing centers represent a unique resource for multidisciplinary and collaborative research between biomedical and behavioral scientists to better understand the complex causes of mental retardation and developmental disabilities. We plan to continue strong support for these centers. To emphasize this I would like to note that, even with a declining budget, core support for the Mental Retardation Research Centers has not been reduced.

Mr. NATCHER. Mr. Roybal?

BUDGET REDUCTION

Mr. ROYBAL. The Institute proposes to cut out $5 million in support of research for mothers and children. Would you please furnish us with a list of research and training activities which have been singled out for cutbacks. For each affected activity, please specify the amount of the decrease.

Dr. SIDBURY. The primary area of reduction in the research for mothers and children program is in the grant component. The reduction of $1.3 million in the pregnancy and infancy activity will curtail research on infant morbidity and mortality, with particular impact on the development of the major research programs for mothers and infants; the sudden infant death syndrome; and the events surrounding the birth process. The reduction of $2.4 million in the growth and development area will reduce our research efforts on the role of nutrition in physiological and intellectual development; the learning process, especially the acquisition of language skills; and the problems of growth and physiological maturation. The reduction of $1.3 million will result in the cutback of our research effort in the prevention and amelioration of mental retardation with particular effect on the research in genetics and inborn errors of metabolism, the early diagnosis of mental retardation, and the social and environmental factors which contribute to intellectual deficiencies.

Mr. ROYBAL. The Institute has pointed out in its "justification" a continuing serious problem in the area of infant mortality. For instance, your data show that in 1973, 55,000 infants died before their first birthday, with over 70 percent associated with low birth weight. Over half of infant deaths after 1 month of age were attributable to crib death. In the light of these facts, what rationale can the Institute provide to justify its request to cut pregnancy and infancy studies by

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$1.3 million? What specific investigations and training efforts will be discontinued or reduced under this proposed decrease?

Dr. SIDBURY. The Institute is proposing a lower budget for research on health problems associated with pregnancy and infancy as part of its overall effort to reduce expenditures. Funds for research on the health problems of pregnant women and infants will be the least affected by fiscal reductions absorbed by the Institute. To accomplish these savings, the Institute will selectively award funds to competing grant applications, National Research Service Awards, and research and development contracts. Areas of research primarily involved in these decreases include studies of factors which contribute to mortality and morbidity during the birth processes, pursuit of leads aimed at identifying infants at risk for SIDS, and full implementation of major research programs for mothers and infants.

Mr. ROYBAL. In the area of growth and development, the Institute has singled out for special attention in 1977 four critical problems: Nutrition and malnutrition; learning disabilities; impact of children illness on child development; and problems of growth and physiological maturation. Since the Institute is also proposing a $2.4 million cut for growth and development, I would appreciate a breakdown of the funding levels for each of the four problem areas as proposed for fiscal year 1977 and funded in fiscal year 1976.

Dr. SIDBURY. Although the total growth and development effort would be reduced by $2.4 million, specific reductions for these four areas are less severe. In the specific research area of nutrition and malnutrition the 1976 estimate of $2.7 million will be reduced by approximately $300,000, down to $2.4 million in 1977. In the learning disabilities research activity the 1976 level of $4.6 million will be reduced by approximately $500,000, down to about $4.1 million. Studies of the impact of childhood illness on child development will be funded at about $2.4 million in 1976; in 1977, the budget request includes $2.2 million, a reduction of $200,000. Research on the problems of growth and physiological development will be reduced from approximately $5.1 million in 1976 to $4.6 million in 1977, a reduction of $500,000.

RESEARCH RELATED TO CHILD ABUSE AND NEGLECT

Mr. ROYBAL. I understand that the Institute currently supports research and training grants relating to child abuse and neglect in the amount of $350,000. Would you provide us with a breakdown of currently funded projects, and their results? What working relationship has the Institute established with health, educational, and public safety institutions toward ameliorating this problem? What funding support will the Institute provide on child abuse and neglect in fiscal year 1977?

Dr. SIDBURY. The National Institute of Child Health and Human Development is supporting research and training grants which are relevant to child abuse and neglect. These projects deal primarily with maternal-infant interaction: studies on how an infant's reaction or response to his or her parents influences the relationship between the parents and the child; how the parent-child interaction affects the infant's emotional, social, and cognitive development. By knowing the

factors which influence normal interaction between the parents and the child, it will be possible to detect deviant behavior which may lead to abnormal parent-child interaction which could result in child abuse.

At the present time, the Institute is supporting seven such projects in an amount totaling $341,436. All of the projects are concerned with mother-infant interactions and the development of the child as an outcome of these interactions. The research covers both normal and handicapped children. Five of the projects are in their first year of support and two are in their second year. There are no results reported as yet, since they are still in the developmental stages. A listing of the projects is provided for the record.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT—PROJECTS WHICH HAVE RELEVANCE FOR CHILD ABUSE AND/OR NEGLECT

Project No.	Principal investigator/institution/location	Title	Current funding	Fiscal year of funds
R01 08109-01A1	Pollitt, Ernesto; Massachusetts Institute of Technology; Cambridge, Mass.	Infant and maternal behaviors regulating early growth.	$45,330	1975
R01 08533-02	Slaughter, Diana T.; University of Chicago; Chicago, Ill.	Study of parent-education programs	89,723	1975
R01 09003-01	Schaffer, Earl S.; University of North Carolina; Chapel Hill, N.C.	Hospital and home support for maternal attqchment.	121,297	1975
R01 09205-01	Chappell, Patricia F.; Boston University; Boston, Mass.	Infant control of caretaker behavior	42,486	1975
F22 02144-02	Mahoney, Gerald J.; University of Rochester; Rochester, N.Y.	Language acquisition of mentally retarded children.	13,400	1976
F32 05067-01	White, Sheila J.; City University of New York; New York, N.Y.	Study of language development in impaired children.	16,200	1975
F32 05204-01	Scholz, Susan C.; University of Miami; Miami, Fla.	Mother-child interactions in handicapped infants.	13,000	1975
Total			341,436	

We have designated two members of our scientific staff to serve on the National Advisory Board on Child Abuse and Neglect which was established by the Secretary, HEW in compliance with the Child Abuse Prevention and Treatment Act. Public Law 93–247. The Board meets monthly for the purpose of assisting the Secretary in coordinating programs and activities related to the prevention, identification, and treatment of child abuse and neglect. Among the 15 agencies represented are the Office of Child Development, the National Institute of Mental Health, the Office of Education, the National Institute of Education, and the Department of Justice.

The estimated 1977 funding for NICHD support of research which has relevance for child abuse is $354,000.

IRON DEFICIENCY ANEMIA

Mr. Roybal. What level of support will the Institute provide for determining the effect of malnutrition or anemia on learning and emotional performance among children? What cooperative arrangements have been established with the following agencies in assessing and alleviating this problem: the National Institute of Education, the Bureau of Community Health Services, the National Institute of Mental Health, the Office of Child Development, and the Department of Agriculture?

Dr. SIDBURY. The problem of malnutrition is less severe in the United States than in many other parts of the world, but we need a more complete understanding of the sometimes subtle ways in which even moderate levels of malnutrition may interfere with learning and emotional development in children. The National Institute of Child Health and Human Development is the lead agency in the support of research in these areas. One of the most prevalent nutritional problems in this country is that of iron deficiency anemia in infancy and adolescence. Research is being supported to pinpoint the cognitive and emotional consequences of this particular nutritional deficit. Fiscal year 1975 funding in these areas totaled $1,563,000. Projections for 1976 are $1.7 million and for 1977 $1.6 million.

In addition, the Institute supports, on a collaborative basis with the United States-Japan cooperative medical sciences program, several other research endeavors concerned with these important problems. Current support for these projects amounts to approximately $158,000, a level which is expected to be maintained over the next couple of years.

Although the National Institute of Child Health and Human Development is the focal point for research on malnutrition in the NIH, Institute staff have been keenly aware of the importance of maintaining contact with other components of NIH and with other Government agencies which are also concerned. The DHEW Nutrition Coordinating Committee serves a useful purpose in this respect as it also includes liaison representatives from non-DHEW agencies such as the Department of Agriculture. Through this means a large number of agencies were kept informed of each others' activities in the area. Discussions are held with other agencies, such as the Office of Child Development and the Food and Drug Administration, when plans are developed for the initiation and funding of new projects in order to avoid unnecessary duplication of effort. Communication with the Maternal and Child Health Service is frequent, and the National Institute of Child Health and Human Development and the Maternal and Child Health Service are well aware of each other's activities and interests.

In addition, there is an NIH nutrition task force whose purpose is to strengthen and coordinate research on nutrition within this agency.

PARENTAL DEPRIVATION

Mr. ROYBAL. The Institute supports research work on the effects of parental deprivation on infants. I have heard of a number of important studies concerned with serious impairment of the infant's social and emotional health as a result of deprivation of affection or stimulus. What level of support is currently provided in this area? How much would be available under the proposed budget? What steps have the Institute taken to disseminate research results to relevant institutions? What contacts have been made with State and local health institutions to develop techniques which would maximize stimulus and interaction for infants?

Dr. SIDBURY. Support of research on parental deprivation in 1976 is estimated at $750,000. If new meritorious research grant applications which are relevant to problems of parental deprivation are

received, the Institute would spend approximately $700,000 in this area in 1977.

In disseminating research results, the National Institute of Child Health, and Human Development participated in the planning and support of a conference on early intervention for high risk infants and young children sponsored by the President's Committee on Mental Retardation and the Association of Childhood Education International, held in May 1974. The Chief of our Mental Retardation and Developmental Disabilities Branch was responsible for the editing and publishing of the conference proceedings. The purpose of this conference was to delineate the state of the art of early intervention for high risk infants and young children. This conference brought forward the current activities and needs in the areas of research, diagnosis and early identification, and methods of child and family intervention which undergird early intervention programs. This effort was aimed at providing the Congress, concerned agencies, the scientific and lay communities with a clear and accurate picture of the state of the art of early intervention for high risk infants. The proceedings of this conference are being published in the book, "Early Intervention for High Risk Infants and Young Children." This publication is one of the Institute's publications in the Mental Retardation Research Center's conference series.

The President's Committee on Mental Retardation, which receives Institute support, has published a digest of the conference proceedings under the title: "What Are We Waiting For." Dissemination of information on research advances on deprivation is implemented routinely by the information dissemination programs of the Mental Retardation Research Centers.

Dissemination of research information to health service institutions is also achieved through communication of research results to representatives of the Office for Maternal and Child Health and the Office of Child Development who are ex-officio members of the National Advisory Child Health and Human Development Council.

Regarding contact with State and local health institutions to develop techniques which would maximize stimulation and interactions for infants, 6 of the 12 Mental Retardation Research Centers have programs on the problem of deprivation. These Mental Retardation Research Centers are administratively and functionally linked to University-Affiliated Facilities. These University-Affiliated Facilities provide training for professionals of all disciplines in clinical applications and the delivery of services. They work closely with State Developmental Disabilities Councils. This linkage of Mental Retardation Research Centers with University-Affiliated Facilities provides for the ready translation of new research findings to the delivery of health services.

Contacts with other State and local health institutions are achieved through liaison of staff with the Office of Child Development and the Office for Maternal and Child Health which have extensive service programs concerned with child development.

RESEARCH TRAINING

Mr. ROYBAL. The Institute proposes to cut training activities by over $1.8 million. How many trainees are expected to receive support under

the proposed budget and in what areas; how does this compare to fiscal year 1976?

Dr. SIDBURY. When comparing the total training program amount in 1976 with the 1977 amount, there is an overall decrease of over $2 million. However, the net reduction occurs only because of the phase-out of the old training grants program. Actually, the new National Research Service Awards program has an increase of approximately $100,000.

In the population research program, the 98 National Research service award trainess, included in the 1977 budget at $1,401,000, represent an increase of 11 trainees and $66,000 over the 1976 budget. Also in this program, the 69 old training grants programs trainees, included in the 1977 budget at $960,000, represent a decrease of 41 trainees and $432,000 from the 1976 budget. The total training budget requirement for the population research program is 167 trainees, for $2,361,000 in 1977.

In the research for mothers and children program, the 147 National Research service award trainees, for $2,147,000 in the 1977 budget, represent an increase of $31,000 over the 1976 budget. Also, in this program, the 207 old training grants program trainees, at $2,837,000 in the 1977 budget, represent a decrease of 145 trainees and $1,835,000 from the 1976 budget. The total training budget requirement for the research for mothers and children program is 354 trainees for $4,984,000 in 1977.

Mr. NATCHER. Mr. Conte?

PERINATAL BIOLOGY CENTER

Mr. CONTE. Doctor, I was very pleased to hear of the opening of the special care nursery. What do you see as the prospects for this facility?

Dr. SIDBURY. We conceive of this unit as a resource for the Clinical Center of the NIH where infants admitted for special studies for any research institute will be hospitalized. The nursery has the appropriate equipment and facilities, specially trained nurses and pediatricians to provide the unique care required by small infants and as additional resources, both positions and funds, are made available we anticipate fully activating the unit to accommodate 20 high-risk infants. The particular studies addressed in this unit by the staff of the National Institute of Child Health and Human Development include studies to determine optimal nutritional requirements of the premature and small infants, the study of problems of malabsorption in small infants and a variety of inborn errors of metabolism. We sincerely hope that the knowledge gained from the research endeavors undertaken in the Perinatal Biology Center will eventually help to continue to reduce this Nation's infant morbidity and mortality rates.

NUTRITION AND PREGNANCY

Mr. CONTE. Does the research of your institute also approach child health from the angle of the pregnant mothers nutritional condition?

Dr. SIDBURY. The Institute is in its 7 year of support of a contract to study the impact of protein-calories nutritional supplementation during pregnancy on the birth weight and development of offspring. Subjects under study are women from Harlem, N.Y., selected on the basis of criteria known to be associated with high vulnerability to low

birthweight children and complications of pregnancy. Low birthweight is an important etiological antecedent to mental retardation in disadvantaged population; however, the contribution of malnutrition to this phenomenon is somewhat obscure. Our research goal is to determine whether these adverse consequences can be prevented by improving the nutritional status of these women.

We are also developing methods and indices for assessing the nutritional status of the pregnant woman and of her fetus. Animal models are utilized to study normal baseline levels during pregnancy for blood constituents. Results from such studies will enable us to better understand the meaning of any deviation under nutritional or physiologic stress and thereby lead to the development of suitable interventions, either through adjustment of the total nutrient supply or of specific nutrients such as trace minerals which can have a major impact on developmental or congenital abnormalities.

Early adolescent pregnancy is associated with a high incidence of perinatal mortality. In view of the increasing numbers of adolescent pregnancies in the United States, the Institute is directing special attention toward the nutritional requirements of adolescent mothers. Studies concerning fetal nutritional needs in combination with the increased requirements of the developing body of the young mother are particularly being encouraged. Complemental to these studies, we are supporting such fundamental investigations as nutrient transport across the placenta, and the role of vascular dysfunction in intrauterine malnutrition. In addition, investigations are also underway to explore the nutritional factors contributing to development of the fetal endocrine system which may have long-term consequences for the health, growth and development of the infant and child.

SUDDEN INFANT DEATH SYNDROME

Mr. CONTE. Can you expand further on the indicators surrounding SIDS; as you know this is an area of particular concern to me?

Dr. SIDBURY. We are finally convinced that there is no single mechanism involved in the sudden infant death syndrome. Scientists have shown recently that specific enzymes having to do with glucose formation in one group of infants is markedly decreased. In some of the infants who have died, there is evidence from the pathology in the lungs that the arterial muscle had thickened. This indicates that the victims had been under low-oxygen stress for a period of time. Other related indicators recently reported include: Abnormal breathing patterns; an immunological defect; abnormal heart beat patterns; and windpipe constriction resulting from, if you will, an overreaction to milk and to glucose. In summary, it now appears that many victims suffered from subtle neurological, cardiorespiratory, and metabolic defects. These are important developments and I am glad that you asked your question. I firmly believe that we are rapidly approaching the time when we will be able to identify potential SIDS victims. If this is accomplished, prevention or treatment measures can be developed and utilized. At this time I wish to submit for the record a special report on the sudden infant death syndrome which covers in greater detail the Institute's efforts in this area.

[Clerk's note: This report appears with other special reports at the end of this volume.]

CONTRACEPTIVES

Mr. CONTE. There has been quite a bit in the news about various side effects of contraceptives. Things such as liver ailments and others. Have you been working on this area?

Dr. SIDBURY. The contraceptive evaluation program of the Institute's Center for Population Research supports research on the adverse effects of contraceptives. One large area of continuing interest is the general surveillance of the health effects of the oral contraceptives, including the risk of birth defects among children conceived during or shortly after the use of oral contraceptives, and the risk of high blood pressure among users. We will be undertaking projects on the risk of heart attacks, liver tumors, and diabetes among oral contraceptive users. Past research has been done on the risks of breast and endometrial cancer and thromboembolism related to oral contraceptive use, and these are areas which may require further investigation.

Mr. CONTE. What alternatives to the female contraceptives we have now do you see down the road? I remember last year, we talked about the possibility of male birth control substances?

Dr. SIDBURY. The contraceptive development program of the Institute's Center for Population Research is fostering research on a number of alternatives to the contraceptive methods currently available.

The development of better methods of natural family planning is being pursued. A large-scale clinical trial has been undertaken to compare the ovulation, or cervical mucus, method with the temperature method; and research is continuing on the development of reliable predictors of the fertile phase of the menstrual cycle. Since these methods do not employ either contraceptive drugs or devices, their only risk is pregnancy.

Investigation of the feasibility of using naturally occurring hormones in contraceptives, instead of the synthetic hormones now used, is underway. A greater margin of safety can be expected from the natural substances.

The synthesis and testing of a new class of compounds which can block the release of eggs from the ovary are also underway. Research is also progressing on the development of methods to reduce the dosage of the currently available oral contraceptives, to increase their safety without a sacrifice in efficacy.

Clinical trials are in progress to test the efficacy of several drugs in blocking sperm production. New drugs are continuously being sought that can block sperm production without undesirable side effects.

POPULATION RESEARCH FUNDING

Mr. CONTE. The justification states that the decrease of $2,636,000 will allow continued efforts in population research. At what level will this research continue? What will be cut?

Dr. SIDBURY. The population research program in 1977 will continue at a level of $45.2 million. No specific projects or research programs will be terminated under the budget planned for 1977; rather, the reduction will be taken across the board and will affect our research efforts in contraceptive development, contraceptive evaluation, social and behavioral sciences, and research fundamental to population sciences.

Mr. CONTE. What new efforts in population research could be initiated if there were not this decrease?

Dr. SIDBURY. In contraceptive development, efforts would continue in the areas of drug and device development for both male and female contraception, and research on natural family planning techniques. The contraceptive evaluation program would further research particularly on the noncontraceptive effects of the oral contraceptives, and risks associated with the use of foams and interuterine devices. Teenage illegitimacy, the consequences of family size and childbearing patterns, and motivations for family planning would remain the focus of the behavioral sciences program. We would continue to explore a broad range of research areas in the field of reproduction, including male and female fertility, fertilization, reproductive endocrinology, and reproductive behavior and diseases.

DECREASE FOR RESEARCH FOR MOTHERS AND CHILDREN

Mr. CONTE. When roughly 8 percent of the infants born in the United States are born underweight and 60,000 low-weight babies have lifelong disabilities, why is there a $5,036,000 decrease for research for mothers and children?

Dr. SIDBURY. The net reduction for the Institute in 1977 is $6.7 million. As a result of this overall reduction, the research for mothers and children program was reduced $5 million. Research concerning the low-birth-weight infant is considered a high priority area by the Institute. Therefore, in the allocation of the reduction within the research for mothers and children program, the pregnancy and infancy research area was not cut as severely.

REDUCTION OF POSITIONS

Mr. CONTE. Why were 13 positions eliminated under laboratory and clinical research? What types of positions were they?

Dr. SIDBURY. The department will soon release, as I understand it, the positions added as a result of the enactment of the 1976 appropriation. The increased positions for laboratory and clinical research in the 1976 Appropriation Act will be primarily assigned to expand the clinical aspects of our new perinatal biology center. The reduction in positions in 1977 is part of the program to reduce Federal employment. The position reduction will be accomplished by attrition in the intramural research programs excluding the perinatal biology center. Therefore, both our intramural efforts in population and reproduction research and maternal and child health research will be affected. The types of positions that will be affected include independent research investigators and technical support staff.

ENVIRONMENTAL RISKS IN PREGNANCY

Mr. CONTE. Are there any indications that environmental factors or substances inhaled by the mother, may result in an increased risk of child abnormalities?

Dr. SIDBURY. The incidence of congenital anomalies has been estimated as high as 7 percent of all live births. It is important to note that the majority of the defects are the result of still unidentified causes. However, there is compelling evidence that certain pollutants

and toxic substances in the environment present increased risks for child abnormalities. Our current knowledge suggests that there are few substances, inhaled by the mother, that have been shown to cause abnormalities in the child. This is not to stay that others do not exist. Some notable examples which do present increased risks are lead, infectious agents, and cigarette smoking. Lead inhaled by the mother has been associated with increased numbers of spontaneous abortions. Women who smoke cigarettes during pregnancy have long been known to have a larger proportion of premature and low birth weight infants than do women who do not. Although low birth weight infants are known to suffer a neonatal mortality rate more than 20 times as high as heavier infants, there has been no such increase in neonatal mortality rate for infants of smokers in most studies. However, one large retrospective British study based on 17,000 births did show an increase in perinatal mortality rates among smokers. This contradiction may indicate there is no simple cause and effect relationship between smoking and pregnancy outcome and that it is necessary to investigate other genetic, environmental and behavioral variables as well. Infectious agents should also be considered as substances inhaled by the mother and capable of causing abnormalities in the infant. These include the rubella virus as well as toxoplasmoisis, both of which are known to produce physical defects.

We continue to maintain an interest in the effects of chemical pollutants on the developing fetus and child. A conference on this subject matter was supported by this Institute in June 1973. Since this is a difficult research area to study, the following points must be considered. The whole aspect of developmental timing is important in studying the effects of chemicals since the fetus may be susceptible to a particular chemical only for a short period during the entire gestation. When considering inhaled environmental substances, it must be pointed out that inhalation of compounds can produce arterial concentrations much higher than can be achieved by absorption through the gut and transport through the liver before reaching the placenta.

COORDINATION OF GENETICS RESEARCH

Mr. CONTE. Is NICHD working with the Institute of General Medical Science on genetic causes of infant mortality and abnormality?

Dr. SIDBURY. Yes, sir. In fact, human genetics undergirds all investigations in the areas of the National Institute of Child Health and Human Development's responsibility. Embryogenesis, the prenatal period, infancy, childhood, adolescence, and early adulthood are gentically interrelated in important and compelling ways. The circumstances of pregnancy, birth, and other life span events determine the nature and quality of an individual's entire life. Therefore, close coordination with the National Institute of General Medical Sciences is essential to us. The National Institutes of Health provides institutional coordination by many mechanisms such as: the Division of Research Grants' study section review system whereby grant applications are first referred to the appropriate review group and then to the appropriate Institute: various inter-Institute meetings and conferences; and the National Advisory Council system which is focused

on program, or Institute, relevance as well as scientific merit. The National Institutes of Health has established an inter-Institute committee on the low birth weight infant which provides for National Institute of General Medical Sciences membership and input on this problem, as it relates to infant mortality and abnormality. Dr. Kretchmer has met with Dr. Kirschstein, Director of the National Institute of General Medical Sciences to establish each Institute's roles concerning genetic research. In the future, we will be looking for gaps in knowledge so that the appropriate Institute can attempt to fill such gaps.

Mr. FLOOD. I thank you very much. I might say you did very well for a sudden appearance on a very tough spot. You should feel very pleased with what you did.

Dr. SIDBURY. Thank you very much. It has been a pleasure.

JUSTIFICATION OF THE BUDGET ESTIMATES

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	1977 Estimate
Appropriation	$126,889,000	$129,883,000
Request pending	9,515,000	---
Subtotal, appropriations	136,404,000	129,883,000
Comparative transfer from:		
"Office of the Director, NIH" for Standard Level User Charge (SLUC)	169,000	---
Total, obligations	136,573,000	129,883,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $55,000; 1977 - $55,000.

National Institute of Child Health and Human Development

Budget Mechanism

	1976 Number	1976 FTE A/	1976 Amount	1977 Number	1977 FTE A/	1977 Amount
Grants						
Regular						
Non-competing	892		$ 58,328,000	878		$ 60,373,000
Competing	139		10,462,000	83		6,435,000
New	144		8,597,000	85		5,450,000
Supplemental	(30)		600,000	(30)		600,000
Subtotal	1,175		77,987,000	1,046		72,858,000
Special						
Mental retardation research centers	12		5,608,000	12		5,608,000
Research career programs	73		1,859,000	76		1,940,000
Scientific evaluation	--		207,000	--		253,000
Subtotal	85		7,674,000	88		7,801,000
Total research grants	1,260		85,661,000	1,134		80,659,000
Training Programs						
Fellowships						
Non-competing	118	186	2,872,000	117	185	2,720,000
Competing	--		---	--		---
New	48	48	579,000	60	60	828,000
Supplemental	--		---	--		---
Subtotal	166	234	3,451,000	177	245	3,548,000
Training grants						
Non-competing	67	462	6,064,000	40	276	3,797,000
Competing	--		---	--		---
New	--		---	--		---
Supplemental	--		---	--		---
Subtotal	67	462	6,064,000	40	276	3,797,000
Total training programs	233	696	9,515,000	217	521	7,345,000
Research and development contracts	196		19,754,000	192		19,254,000
Intramural research and direct operations						
Laboratory and clinical research	--		13,190,000	--		13,583,000
Epidemiology and biometry	--		667,000	--		679,000
Research management and program services	--		6,562,000	--		7,031,000
Standard level user charge	--		169,000	--		219,000
Program management	--		1,055,000	--		1,113,000
Total	--		136,573,000	--		129,883,000

A/ Full-time equivalents

DHEW - National Institutes of Health

Crosswalk - 1976 Column 1977 Justification

INSTITUTE: National Institute of Child Health and Human Development
(in thousands)

Program \ Mechanism	Research Grants				Training Programs		Research and Development Contracts	Intramural Research and Direct Operations	Program Management	Total
	Regular Program		Specials							
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Population.....	$22,043	$ 7,176		$ 723	$1,392	$1,335	$15,154			$ 47,823
2. Research for mothers and children (formerly child health).....	36,285	12,483	$5,608	1,343	4,672	2,116	4,600			67,107
3. Intramural research and direct operations.....								$20,588		20,588
4. Program management.....									$1,055	1,055
Total obligations.....	58,328	19,659	5,608	2,066	6,064	3,451	19,754	20,588	1,055	136,573

DHEW - National Institutes of Health

Crosswalk - 1977 Column 1977 Justification

INSTITUTE: National Institute of Child Health and Human Development
(in thousands)

Program \ Mechanism	Research Grants									
	Regular Program		Specials		Training Programs		Research and Development Contracts	Intramural Research and Direct Operations	Program Management	Total
	Non-competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Population.....	$22,362	$ 4,954		$ 731	$ 960	$1,401	$14,779			$ 45,187
2. Research for mothers and children (formerly child health).....	38,011	7,531	$5,608	1,462	2,837	2,147	4,475			62,071
3. Intramural research and direct operations.....								$21,512		21,512
4. Program management.....									$1,113	1,113
Total obligations.....	60,373	12,485	5,608	2,193	3,797	3,548	19,254	21,512	1,113	129,883

Summary of Changes

1976 Estimated Obligations	$136,573,000
1977 Estimated Obligations	129,883,000
Net change	- 6,690,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1976 pay raise and health benefits increases	--	$ 348,000	--	+$ 116,000
2. Annualization of new positions in 1976	--	185,000	--	+ 260,000
3. Within-grade pay increases	--	9,825,000	--	+ 136,000
4. Wage Board pay increases	--	70,000	--	+ 2,000
5. Bureau of Employee Compensation	--	20,000	--	+ 5,000
6. Increased cost of postage	--	184,000	--	+ 30,000
7. Increased service and supply fund costs	--	750,000	--	+ 60,000
8. Federal Telecommunications System.	--	90,000	--	+ 15,000
9. Annualization of travel increases because of per diem changes	--	320,000	--	+ 15,000
10. Increased payment to central activities such as program evaluation	--	1,439,000	--	+ 300,000
11. Payment to "National Institutes of Health Management Fund"	--	6,080,000	--	+ 445,000
12. Standard level user charge	--	169,000	--	+ 50,000
Subtotal	--	---	--	+ 1,434,000
B. Program:				
1. Research Grants:				
a. Regular Program				
(1) Noncompeting continuations converted from competing status	--	58,328,000	--	+ 21,877,000
(2) Competing (new, continuations and supplementals)	--	19,659,000	--	+ 12,485,000
b. Special Programs				
(1) Research career programs.	--	1,859,000	--	+ 81,000
(2) Scientific evaluation grants (for increased costs)	--	207,000	--	+ 46,000
2. Training Programs:				
a. Fellowships				
(1) Noncompeting fellowships converted from competing status and associated increased costs	--	2,872,000	--	+ 650,000
(2) Competing fellowships (new National Research Service Awards)	--	579,000	--	+ 828,000
Subtotal	--	---	--	+ 35,967,000
Total Increases	--	---	--	+ 37,401,000

Summary of Changes - Continued

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Decreases:				
A. Built-in:				
1. One less day of pay	--	$ 7,052,000	--	-$ 27,000
Subtotal	--	---	--	- 27,000
B. Program:				
1. Research Grants:				
a. Regular Program				
(1) Noncompeting completed or converted to competing status	--	58,328,000	--	- 19,832,000
(2) Competing completed or converted to non-competing status	--	19,659,000	--	- 19,659,000
2. Training Programs:				
a. Fellowships				
(1) Noncompeting completed	--	2,872,000	--	- 802,000
(2) Competing fellowships completed or converted to noncompeting status	--	579,000	--	- 579,000
b. Training Grants				
(1) Noncompeting completed	--	6,064,000	--	- 2,267,000
3. Research and Development Contracts: (reduction of effort in population and research for mothers and children contract programs)	--	19,754,000	--	- 500,000
4. Intramural Research and Direct Operations:				
a. Decrease of 23 positions	328	20,588,000	-23	- 425,000
Subtotal	--	---	-23	- 44,064,000
Total Decreases	--	---	-23	- 44,091,000
Total Net Change	--	---	-23	- 6,690,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Pos.	1976 Revised President's Budget Amount	1976 Appropriation Pos.	1976 Appropriation Amount	1977 Estimate Pos.	1977 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
51	Population.....	---	$ 41,999,000	---	$ 47,823,000	---	$ 45,187,000	---	-$2,636,000
55	Research for mothers and children (formerly child health).....	---	59,001,000	---	67,107,000	---	62,071,000	---	- 5,036,000
61	Intramural research and direct operations.	305	20,288,000	328	20,588,000	305	21,512,000	-23	+ 924,000
	Standard level user charge.....		(169,000)		(169,000)		(219,000)		(+50,000)
65	Program management.....	49	1,055,000	49	1,055,000	49	1,113,000	---	+ 58,000
Total obligations.....		354	122,343,000	377	136,573,000	354	129,883,000	-23	- 6,690,000

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	377	354	-23
Full-time equivalent of all other positions	72	75	+ 3
Average number of all employees	434	429	- 5
Personnel compensation:			
Permanent positions	$ 7,670,000	$ 7,755,000	+$ 85,000
Positions other than permanent	580,000	600,000	+ 20,000
Other personnel compensation	290,000	320,000	+ 30,000
Subtotal, personnel compensation	8,540,000	8,675,000	+ 135,000
Personnel benefits	1,285,000	1,310,000	+ 25,000
Travel and transportation of persons	320,000	345,000	+ 25,000
Transportation of things	50,000	50,000	---
Rent, communications, and utilities	320,000	365,000	+ 45,000
Printing and reproduction	215,000	230,000	+ 15,000
Other services:			
Project contracts	19,754,000	19,254,000	- 500,000
Payment to NIH management fund.	6,249,000	6,744,000	+ 495,000
Other	2,639,000	2,831,000	+ 192,000
Supplies and materials	1,575,000	1,625,000	+ 50,000
Equipment	450,000	450,000	---
Grants, subsidies, and contributions	95,176,000	88,004,000	- 7,172,000
Total obligations by object	136,573,000	129,883,000	- 6,690,000

Significant Items in House and Senate
Appropriations Committees' Reports

Item	Action taken or to be taken
1976 House Report	
1. The Committee was concerned that the Perinatal Biology Center, located in the NIH Clinical Center, was only partially operational and directed that adequate resources be made available so that the new facility could be effectively utilized (page 38).	1. The Institute has redirected several positions and a modest amount of funds to the Perinatal Biology Center in order to initiate the clinical aspects of the program. On November 26, 1975, the first infant was admitted to the special care nursery of the Center.

Authorizing Legislation

Legislation	1977 Authorization	1977 Appropriation Requested
Public Health Service Act, Section 301 - Research and Investigations, in general.....	Indefinite	$76,471,000 B/
Public Health Service Act, Title IV, Part E - National Institute of Child Health and Human Development.....	Indefinite	
Public Health Service Act, Title IV, Part I - National Research Service Awards.....	A/	7,345,000 B/
Public Health Service Act, Title X, Section 1004 - Family Planning and Population Research Act of 1975.....	$60,000,000	46,067,000 B/

A/ Authorization expired June 30, 1975; extension legislation is pending.

B/ Funding estimate only.

National Institute of Child Health and Human Development

COMPARABLE

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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 C/	128,271,000	126,067,000
1976	106,231,000	127,058,000	127,058,000	
Items not considered		(9,515,000) D/	(9,515,000) D/	
1977	129,883,000			

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 authorized by P.L. 93-192.

C/ Excludes funds for research and development contracts which were not considered by the House due to expiration of authorizing legislation.

D/ Represents funds for training programs which were not considered due to expiration of authorizing legislation.

NOTES: 1/ Prior to 1975, the budget was presented on a mechanism basis rather than program. Funds within the appropriations for 1967 through 1974 for aging research are not identifiable and, therefore, are included.

2/ The figures presented in this table have been adjusted to reflect the transfer of some major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of General Research Support Grants is no longer the function of this Institute. The amounts originally contained in this account in previous years for this particular program have been removed for comparability purposes.

National Institute of Child Health and Human Development

ACTUAL

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	126,889,000	126,889,000	
Items not considered		(9,515,000) D/	(9,515,000) D/	
1977	129,883,000			

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 authorized by P.L. 93-192.

C/ Excludes research and development contracts which were not considered by the House due to expiration of authorizing legislation.

D/ Represents funds for training programs which were not considered due to expiration of authorizing legislation.

Justification

National Institute of Child Health and Human Development

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Population	---	$ 41,999,000	---	$ 47,823,000	---	$ 45,187,000	---	-$2,636,000
Research for mothers and children (formerly child health)	---	59,001,000	---	67,107,000	---	62,071,000	---	- 5,036,000
Intramural research and direct operations	305	20,288,000	328	20,588,000	305	21,512,000	-23	+ 924,000
Program management	49	1,055,000	49	1,055,000	49	1,113,000	---	+ 58,000
Total	354	122,343,000	377	136,573,000	354	129,883,000	-23	- 6,690,000

General Statement

The mission of the National Institute of Child Health and Human Development (NICHD) 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.

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. The CPR has responsibility for understanding the forces affecting population growth, the development and evaluation 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 on the development of scientific data and theory basic to reproductive biology.

Continued Congressional concern for population and reproduction research resulted in the renewal in fiscal year 1976 of Title X of the Public Health Service Act which specifically authorizes the population research programs of the NICHD. A number of factors justify this emphasis on population research including: 1) the need to develop an array of safe and effective contraceptive methods, so that the contraceptive needs of each couple can be met; 2) the widespread use of contraceptives some of which may not be as safe as once thought; 3) the need to understand how reproductive systems function, how the process might be interrupted for contraception, and how dysfunction of the system can be treated to alleviate infertility; 4) the alarming increase in the numbers of teenage pregnancies, with the concomitant birth of babies at high risk for disease and disability; and 5) the changing patterns of fertility, as influenced by age, work-force participation, and attitudes toward the benefits of smaller families.

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, prevention 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 occurring in the earliest stages through adulthood. The necessity for this problem-oriented research approach is highlighted by the following statistics:

- Although the infant mortality rate has fallen from 22.4 to 17.6 deaths per 1000 live births over the last six years, the United States has dropped from fourteenth to fifteenth position among developed countries.

- Approximately 7.6 percent, or 238,000, of the infants born in the United States in 1973 were born either too soon or too small, weighing less than 5 1/2 pounds. Approximately 42,000 of these babies died within their first month of life.

- Of the low birth weight babies, about 60,000 born each year will have life-long disabilities, including mental retardation.

- Approximately 7,500 infants succumb to the sudden infant death syndrome each year.

- Of all babies born in this country, 3.5 percent show evidence of a birth defect during the first month of life; 7 percent have developed identifiable defects by the end of the first year.

- About 10 percent, or approximately 7 million, children between the ages of 10 and 18 in the United States suffer some major impairment including communicative disorders, learning disabilities and aberrant functional and skeletal development.

- 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.

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.

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Contraceptive Development...	---	$ 6,360,000	---	$ 6,625,000	---	$ 6,460,000	---	-$ 165,000
Contraceptive Evaluation....	---	4,970,000	---	5,179,000	---	5,050,000	---	- 129,000
Directed Behavioral Research.....	---	3,217,000	---	3,350,000	---	3,269,000	---	- 81,000
Research Fundamental to the Population Sciences...	---	27,452,000	---	32,669,000	---	30,408,000	---	- 2,261,000
Total.....	---	41,999,000	---	47,823,000	---	45,187,000	---	- 2,636,000
Budget Mechanism:								
Research Grants:								
Regular:								
Noncompeting.....	339	22,043,000	339	22,043,000	328	22,362,000	-11	+ 319,000
Competing.....	34	2,338,000	104	7,176,000	67	4,954,000	-37	- 2,222,000
Special.....	19	548,000	26	723,000	25	731,000	- 1	+ 8,000
Subtotal.....	392	24,929,000	469	29,942,000	420	28,047,000	-49	- 1,895,000
Training Programs:								
Fellowships.....	66 A/	1,131,000	87 A/	1,335,000	98 A/	1,401,000	+11 A/	+ 66,000
Training grants.....	40 A/	1,392,000	110 A/	1,392,000	69 A/	960,000	-41 A/	- 432,000
Subtotal.....	106 A/	2,523,000	197 A/	2,727,000	167 A/	2,361,000	-30 A/	- 366,000
Research and Development Contracts.....	155	14,547,000	162	15,154,000	158	14,779,000	- 4	- 375,000
Total.....	---	41,999,000	---	47,823,000	---	45,187,000	---	- 2,636,000

A/ Full-time equivalents

Introduction

The Center for Population Research (CPR) has the primary responsibility for Federal research on fertility, reproduction, contraception, and the effects of population growth and change. The research program is concentrated in four major areas: 1) fundamental research in reproductive biology and the behavioral sciences; 2) the development of new and improved contraceptive methods; 3) the evaluation of contraceptive methods currently in use; and 4) research in the social and behavioral sciences to analyze the determinants and consequences of population size, composition and distribution.

This program is accomplished through the award of research grants, including the Population Research Centers; fellowships; training grants; and research contracts.

Program Plans, 1977

The 1977 level, a decrease of $2,636,000 from 1976, will allow for continued efforts in the following activities.

Contraceptive Development - In 1977, clinical trials will be carried out to evaluate new drugs which have been synthesized and tested and which show promise of safe and efficacious application as contraceptives. Significant advances have also been made in the development of contraceptive devices for both men and women, and clinical trials will be undertaken with the most promising of these. Some of these methods to be tested include a reversible vas occlusive device; biodegradable drug delivery systems, designed to release contraceptive drugs into the reproductive system over 6 months or a year; the use of ethynyl estradiol as a post-coital contraceptive; and the administration of synthetic male hormones for male contraception.

Two major testing facilities are now operational for the evaluation of antifertility agents and devices. The biological testing facility is utilized for evaluation of a broad spectrum of new drugs and devices, in order that potential leads in the area of fertility control can be rapidly exploited. The primate testing facility provides subjects for testing drugs and devices before clinical trials are attempted in humans.

Efforts to improve the efficacy of natural family planning techniques will continue in 1977, including such methods as the Billings' technique of evaluating the nature and extent of cervical mucus secretion as a function of fertility. In addition, the effort to develop a reliable, simple, and inexpensive means of ovulation prediction will be continued. The development of a method of contraception not dependent upon drugs or devices will have special appeal to people who, for various reasons, do not wish to or cannot use drugs or devices.

In the program to develop safe and effective contraceptives for men, studies will continue to evaluate the combined effects of two androgenic steroids on sperm production. Results thus far indicate that this application produces greatly lowered sperm counts, which are incompatible with fertility, without affecting libido or later potency. This family planning method can be reversed with simple cessation of treatment.

Contraceptive Evaluation - The focus in 1977 of the program to evaluate fertility regulating methods currently in use will continue to be on the enumeration of hazards associated with their use and the identification of risk factors which increase the likelihood of complications among those exposed to these methods.

One area of particular concern is the oral contraceptives and adverse responses they may produce, particularly in women with risk factors for cardiovascular disease. Our longitudinal study of women on oral contraceptives will continue in 1977 to identify changes related to oral contraceptive use, such as changes in blood glucose, lipid levels, blood pressure, body weight, and blood coagulability. In addition, the recent observation of increased risk of myocardial infarction (heart attack) among these women will be further investigated, particularly in the presence of other factors known to be related to cardiovascular disease, such as obesity, hypertension, diabetes and smoking. The age factor will also be examined, since the risk seems to increase greatly in women over 40. The risk of breast cancer and of cancer of the female genital tract due to oral contraceptive use will also be investigated.

Ongoing projects will continue to explore the relation between various contraceptive methods and birth defects and other adverse manifestations among the offspring of users. Preliminary data have confirmed an increase in congenital malformations among the offspring of women who have been exposed to sex steroids early in pregnancy.

Vasectomy is becoming an increasingly common contraceptive method, and will continue to be evaluated for possible adverse manifestations. Since immune antibodies to sperm increase markedly after vasectomy, the implications for autoimmune disease will be explored.

To fill important gaps in our knowledge, and responding to concerns raised about the safety of intrauterine devices (IUDs) and about techniques used to induce abortions, various projects will be continued in 1977. In addition, scientists will investigate the findings that the risk of prematurity and low birth weight is increased among pregnancies in women who have had prior induced abortions. Because of the widespread use of induced abortion, it is essential to evaluate the risks to subsequent pregnancies.

Directed Behavioral Research - The serious social problems related to teenage illegitimacy are of increasing concern and require continued study in 1977 to understand its causes and consequences, so that the situation can be alleviated. In spite of the availability of contraceptives, the number of teenage illegitimate births increases yearly, and there are now about 200,000 such births a year in the U.S. Such pregnancies have overwhelming social and health consequences, both to the mothers and to their children: the infants of teenagers are at higher risk because of poor prenatal care; the likelihood of lower birth weight is greater; and teenagers who choose abortion do so later in pregnancy, thus increasing their risk.

In order to enhance research already undertaken on the consequences of family size and childbearing patterns, a study will be developed to analyze data to obtain better estimates of the cost of children by income and residential categories. The analysis will focus primarily on the difference in levels of living resulting from variations in the number and spacing of children and age of parents.

A major focus is to understand the factors that motivate couples to control their fertility and the processes by which they go about it. Several studies will be initiated to determine how career aspirations, employment opportunities and experience, and other related factors affect marriage and childbearing patterns. Other studies will focus on the decision-making process of couples regarding fertility-related behavior: how couples set goals, reconcile differences, obtain information about the consequences of having a child, and influence each other in evaluating and choosing methods of fertility control.

The consequences of family size and childspacing for both parents and children will continue to be an area of concern. Recent research reports an inverse correlation between intelligence of offspring and family size, regardless of socio-economic status and intelligence of parents. Research will continue concerning health as a consequence of family size and the spacing of children, and the effects of family size on marital stability and happiness.

Research Fundamental to the Population Sciences - The CPR will continue to support increasingly sophisticated and complex studies in reproductive biology and endocrinology, and in broad basic population processes in the social sciences. A major resource in the ongoing research activity is a productive Population Centers Program. These twelve Centers provide a coordinated, multidisciplinary aggregate of scientists investigating fundamental social and biomedical population research concerns.

Investigations will continue on men, women, and laboratory animals, encompassing a broad range of research areas in the field of reproduction, including female fertility, male fertility, fertilization, gamete transport, reproductive endocrinology, reproductive behavior, and reproductive diseases. A major effort will continue to be aimed at understanding how hormones act in the control of reproduction. It now appears certain that sex steroid hormones act by activation of genes in their target organs, for example, ovary, testis, and uterus. Interference with one or more of the steps in this process could lead to the development of new contraceptive measures.

Studies will continue on the role of the pituitary gonadotropins (hormones) in the control of ovarian and testicular function, in order to provide the theoretical basis for the development of new measures for the alleviation of infertility, and the regulation of fertility for both males and females. In addition, the mechanism of action of progesterone, the hormone of pregnancy, will continue to be investigated, along with the mechanism of sperm production, and the metabolism of steroids in tissues.

New knowledge has recently been added to our understanding of the impact of environmental factors via the brain on reproductive events. In both the male and female, stress-induced increases of the sex steroid hormones from the adrenal gland now appear to have a definite role in modulating control of the gonadotropic hormones which regulate the ovary and testis. Such studies underscore the need to assess the interdependence of other endocrine glands as well as the brain with the ovary and testis in the control of reproductive processes, and will be continued in 1977.

Research for Mothers and Children

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Subactivities:								
Pregnancy and Infancy	---	$20,334,000	---	$23,768,000	---	$22,482,000	---	-$1,286,000
Growth and Development	---	18,500,000	---	21,306,000	---	18,888,000	---	- 2,418,000
Mental Retardation	---	20,167,000	---	22,033,000	---	20,701,000	---	- 1,332,000
Total	---	59,001,000	---	67,107,000	---	62,071,000	---	- 5,036,000
Budget Mechanism:								
Research Grants:								
Regular:								
Noncompeting	553	36,285,000	553	36,285,000	550	38,011,000	- 3	+ 1,726,000
Competing	76	5,321,000	179	12,483,000	101	7,531,000	-78	- 4,952,000
Special	50	6,726,000	59	6,951,000	63	7,070,000	+ 4	+ 119,000
Subtotal	679	48,332,000	791	55,719,000	714	52,612,000	-77	- 3,107,000
Training Programs:								
Fellowships	120 A/	1,891,000	147 A/	2,116,000	147 A/	2,147,000	---	+ 31,000
Training grants	352 A/	4,672,000	352 A/	4,672,000	207 A/	2,837,000	-145 A/	- 1,835,000
Subtotal	472 A/	6,563,000	499 A/	6,788,000	354 A/	4,984,000	-145 A/	- 1,804,000
Research and Development Contracts	30	4,106,000	34	4,600,000	34	4,475,000	---	- 125,000
Total	---	59,001,000	---	67,107,000	---	62,071,000	---	- 5,036,000

A/ Full-time equivalents

Introduction

The goal of the Research for Mothers and Children program (formerly designated "Child Health") is focused on prevention of disease and disability, with the underlying assumption that healthier children will produce the long range benefit of a healthier adult population. The Center for Research for Mothers and Children (CRMC) has been developed to advance knowledge on the psychosocial and biological factors which contribute to the good health of pregnant women, and of children as they develop into adults. The problems of primary interest are infant mortality and morbidity: mortality, because of the tragic loss of life and resulting grief for families; morbidity, because developmental disorders early in life often predispose to disease or disability later. A major concern is achieving understanding of the causes of acute and chronic disabilities associated with the process of human development, in order to find means of preventing them. Special attention is given to the multifaceted problem of mental retardation.

This program is accomplished through the award of research grants, including Mental Retardation Research Centers and Major Research Programs for Mothers and Infants; fellowships; training grants; and research and development contracts.

Program Plans, 1977

The 1977 level, a decrease of $5,036,000 from 1976, will allow for continued efforts in the following activities.

Pregnancy and Infancy (formerly Perinatal Biology and Infant Mortality) - This program is committed to the promotion of a coordinated research effort which will result in the development of new knowledge about pregnancy and maternal health, embryonic and fetal development, and infant health and survival through the first year of life. Research goals include the prevention or amelioration of health problems that contribute to both maternal and infant morbidity and mortality, and narrowing the gap between the identification of new knowledge and its incorporation into health care delivery.

A major concern is the prevention of low birth weight infants (less than 5.5 pounds). In this country in 1973, of more than 3 million babies born alive, 55,000 infants (18 of every 1,000) died before their first birthday. More than 70 percent of these infant deaths, occurring predominately during the first 28 days of life, were associated with low birth weight. 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. Low birth weight infants frequently derive from mothers who are adolescent, malnourished, or afflicted with chronic diseases such as toxemia or hypertension. Other high risk infants are born to mothers who have diabetes, a genetic disorder, or a poor reproductive history. Another concern is with the infants whose deaths are attributable to crib death (the sudden infant death syndrome - SIDS). Of the more than 13,000 infants who died in 1973 after one month of age, it is estimated that more than half succumbed to SIDS.

To address the critical health needs of mothers and infants, the Institute is developing a comprehensive research effort directed toward assuring better maternal and infant health and well-being. Major Research Program's (MRP's) for Mothers and Infants will be organized around problem oriented health themes related to prevention, treatment, or amelioration of disorders and diseases

associated with pregnancy, infancy, and with human development through young adulthood. Areas of emphasis include, but are not limited to gestation; embryonic and fetal development; infant risk of morbidity/mortality; and handicapping conditions of childhood.

In 1977, continued emphasis will be given to increasing our knowledge about why babies are born prematurely and to identifying environmental and genetic factors which contribute to the birth of babies who are small for their gestational age. These research efforts will build upon knowledge gained in past years.

For example, it has been observed that the metabolic state of some high risk pregnant women acts to prevent the transfer of oxygen across the placenta from mother to fetus. This metabolic condition can be dangerous to the pregnant woman toward the end of her pregnancy and can retard growth of the fetus. Moreover, as a result of a study of the transfer of sugar and other active substances from mother to fetus during the last three months of pregnancy, it appears that under some conditions inhibition of fetal growth may be related more to inability of the placenta to adequately transport these molecules than to insufficent maternal nutrition.

Research pertaining to high risk pregnancy and to fetal growth retardation will, therefore, concentrate on several key issues. Since maternal conditions such as cigarette smoking and high blood bicarbonate can influence fetal growth, the contribution of maternal diseases and disorders to growth retardation in the fetus will be studied. Further research on placental damage (structural or functional) and effects of such damage on fetal growth and development will be undertaken. Maternal stress and its effects on the metabolism of mother and fetus and on the initiation of labor will be considered, especially as related to prematurity.

Further information will be sought during 1977 about the interaction of genetic, physiologic, chemical and environmental factors which may contribute to abnormal embryonic development resulting in either malformed or disabled children. Therefore, research will be focused on areas such as the sensitivity of the developing human embryo to chemical compounds ingested by, injected into, or inhaled by the mother.

As a result of continuing research efforts, there is a growing body of evidence that the victims of SIDS are not completely normal and their deaths not as inexplicable as was once thought, but rather that these infants have subtle physiological defects. Recent observations of pathological changes in the victims support the hypothesis that sleep apnea (frequent nonbreathing periods) and consequent oxygen deficiency are critical elements in many cases of SIDS. Thus, it may eventually be possible to detect potential SIDS victims and prevent them from dying. Research efforts will be directed toward the identification of infants who could be susceptible to SIDS and to possible preventive approaches.

Growth and Development - This program is concerned with the period of human growth and development from infancy through adolescence to maturity. Since the key to adult health and the development of full human potential lies in understanding the mechanisms of human growth and development, the goal of the program is to broaden our understanding of the interplay of biological, intellectual and social factors that determine the emergence and development of the competent, healthy individual. Four critical problems have been identified for special attention in 1977: nutrition and malnutrition; learning disabilities; the impact of childhood illness on child development; and problems of growth and physiological maturation.

Program emphasis has been placed on nutrition and malnutrition because health related nutrition problems affect millions of persons in the U.S. and hundreds of millions of people around the world. Attention will be given to studies of the effects of nutritional deprivation in early life on the mental development and physical performance of pre-school and elementary school children. These research efforts would be directed toward gaining the knowledge base necessary for the ultimate development of effective intervention or clinical treatment of these critical problems.

Although many studies focus on severe protein calorie malnutrition, attention has been turned recently to iron deficiency anemia which is the most common nutritional problem among infants and adolescents in this country. Available information on anemia and behavior suggest that the consequences of iron deficiency are likely to be reflected in behavior factors such as attentiveness, curiosity, activity and responsiveness.

Obesity as it has its origins in early childhood continues to be a concern in 1977. Increasingly, young children are found to be overweight and inactive, and it is known that the overweight individual is much more prone to heart disease, hypertension, and other chronic diseases. Recent evidence indicates that nutritional manipulation very early in life can permanently influence the number of fat cells in the body. This may provide an effective approach to prevention of obesity.

Another major research area focuses on both learning and cognitive development and on specific learning disabilities. Learning and cognitive development research explores the general mechanisms and processes that serve as the basis for understanding a variety of learning problems. In addition, research is targeted to specific learning disabilities, that is, those individuals with special language dysfunctions reflected primarily in difficulties in acquiring and using the spoken word and in learning to read, to use written language, to spell, to tell time or to calculate.

An area selected for high priority for 1977 is research related to dyslexia, a term used to describe a special learning dysfunction reflected in reading failure. Continued support of fundamental research into the reading process will further our understanding of how the reading skill is acquired and how it is overlaid on one's spoken language. This information will lead to a better understanding of the normal reading process and those factors which interfere with or prevent many children from acquiring this essential skill.

In 1977 investigations will continue into the impact of childhood illness on child development. A crucial function in normal growth and development is the ability of the human organism to protect itself in a hostile external environment through its immunologic system (total body defense system against disease).

The immunologic immaturity found in premature infants is an important area of consideration, since these infants are particularly vulnerable to increased morbidity. Infection is unquestionably one of the major health problems encountered in the perinatal period.

The effects of chronic illness on non-ill siblings will also be investigated. Accumulating anecdotal evidence suggests that so many family resources are spent on the sick child that the nondiseased sibling may be affected detrimentally as a result. Thus the impact of the many chronic illnesses which modern medicine can treat in part or prolong may be extended into other family members thus adversely influencing their assumption of adult roles.

Because of the smaller blood volume in infants and children, microassay techniques to monitor dosage and diagnose toxicity are needed for potent new drugs in common use in pediatric populations. An investigator has perfected a microassay technique using 0.1 milliliter of blood for the monitoring of digoxin (a drug used to combat heart disease) dosage and diagnosis of digitoxicity. This relatively new technique of radioimmunoassay makes feasible microassays for a number of drugs and will help prevent the occasionally disastrous complication of wrong drug dosage.

Problems of growth and physiological maturation to be investigated in 1977 include the basis for hereditary disease, developmental abnormalities and endocrine diseases of childhood. Continued support of the sophisticated and complex studies related to these dysfunctions will ultimately yield the information needed to prevent their occurrence.

Mental Retardation - The objective of the program is to develop and support research aimed at the prevention of mental retardation and, when this is not possible, to effect its amelioration. In implementing its preventive and ameliorative research efforts, the program also supports research concerned with other developmental disabilities. Its research efforts with premature and low birth weight infants, genetics, and infectious diseases, among others, apply directly to the prevention of the full range of developmental disabilities. Efforts to ameliorate mental retardation, particularly in the area of early care, training and education have general applicability to all of the recognized developmental disabilities.

This program has the responsibility for the twelve Mental Retardation Research Centers. The Centers represent a unique resource for multidisciplinary and collaborative research between biomedical and behavioral scientists to better understand the complex causes of mental retardation and developmental disabilities. This concentration of research talent in mental retardation and developmental disabilities is the Nation's response to these major social problems.

Research in genetics and inborn errors of metabolism continues as a priority research area. Well over 60 mental retardation syndromes have been identified as having genetic origin. It has been estimated that genetic defects are present in 5 percent of all live births; over one-third of all spontaneous abortions are associated with chromosomal defects; and about one-third of all admissions to hospital pediatric wards are for genetic reasons. In institutions for the mentally retarded today, about 5 percent of the patients have inborn errors of metabolism, over 10 percent have Down's syndrome (mongolism), and 25 percent have central nervous system defects, many of which are inherited. Most of these genetically determined conditions are associated with mental retardation or defects which impair a child's ability to achieve his optimal development. Activity in this field will be encouraged in 1977 with emphasis given to moving genetic knowledge and developments into service. An automated system for chromosome analysis has been developed recently. Plans now call for field testing the device to ready it for commercial production. Final development should result in an instrument useful in mass screening for genetic defects at greatly reduced costs, and in research, clinical, and epidemiological applications.

Developmental disabilities are often the result of reproductive casualty stemming from disorders of pregnancy, complications of birth, and ill health of the mother. A major deterrent to research progress in this field, follows from limitations of current instruments and methods for assessing early developmental fault. Emphasis in 1977 will be placed on developments which might help achieve

early identification of infants at risk for faulty development, which open up opportunities for early corrective intervention, and which can be related back to the conditions of pregnancy resulting in reproductive casualty.

Research support is planned to facilitiate new developments in the field of infant learning and the response of risk infants to meaningful interventions by professionals, parents and caretakers. The application of behavior modification principles and techniques continues to yield significant findings in the treatment of retardation.

Areas of emphasis include not only the biological aspects of mental retardation, but the behavioral and social aspects as well. Among the various handicaps shared by the mentally retarded and developmentally disabled, communication disorders are the most pervasive. At least 20 percent of the retarded have significant hearing impairments, over 70 percent have significant speech problems and almost all have some type of language disorder. Research efforts are now, and will be, directed toward understanding the effect of hearing impairment on speech and language development and the impact of speech and language problems on the mentally retarded. Advances have been made in the assessment of hearing abilities during the first year of life which has major significance for early intervention programs.

Language is one of the most significant skills requisite to the placement of a retarded person back in the mainstream of our social system. With continued research on speech and language, it is rapidly becoming possible to design intervention systems which will change the lives of thousands of retarded persons who would otherwise have lived their lives in isolation from functional communications skills.

Intramural Research and Direct Operations

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Budget Mechanism:								
Laboratory and Clinical Research.....	170	$12,990,000	183	$13,190,000	170	$13,583,000	-13	+$393,000
Epidemiology and Biometry...	15	667,000	15	667,000	15	679,000	---	+ 12,000
Research Management and Program Services.....	120	6,462,000	130	6,562,000	120	7,031,000	-10	+ 469,000
Standard Level User Charge..	---	169,000	---	169,000	---	219,000	---	+ 50,000
Total.....	305	20,288,000	328	20,588,000	305	21,512,000	-23	+ 924,000

Introduction

The Intramural Research and Direct Operations program comprises (1) the Institute's intramural effort, including epidemiology and biometry, in the major program areas of population and reproduction, and maternal and child health and (2) the scientific and administrative staff responsible for grant and contract programming, review and administration, and analysis of the Institute's programs.

Program Plans, 1977

Laboratory and Clinical Research:

The net increase of $393,000, consists of a program decrease of $250,000 and a mandatory decrease of $13,000 for one less day of pay in 1977; offset by an increase of $329,000 for mandatory increases such as annualization of pay raise and within-grade increases and $327,000 for payment to NIH Management Fund for centrally furnished services. The 1977 level for positions was reduced by 13.

Population and reproduction - The thrust of this endeavor is a better definition of the details relating to the reproductive processes in both male and female. There has been a continuing accumulation of knowledge and facts about these processes which has lead scientists to believe that they are nearing totally new and potentially more effective approaches to the understanding and control of fertility and infertility problems.

Studies have provided evidence that antibodies to a portion of a hormone (gonadotropin) can be used to detect the hormone in the urine of pregnant women as early as the 8th day after conception. This modified assay is more sensitive than those previously reported. It can be synthesized and hence produced commercially. It is hoped that this will lead to a simple, quick, and specific test for pregnancy which can be carried out in any physician's office. This early diagnosis should lead to earlier and better prenatal care as well as easier problem identification such as would be the case in an ectopic (tubal) pregnancy.

In 1975 it was found that the monkey has a menopause, hence scientists have the first animal model to study this phenomenon of the female reproductive system.

Evidence has been deduced demonstrating that male hormone mediates hormone production in the ovary and that the male hormone appears in the nucleus of the cells of the ovary. This observation provides a means of examining estrogen (a hormone) production in a more sophisticated manner than heretofore. This hormone is essential to fertility and knowledge regarding estrogen is essential to understanding fertility control.

The programs of the Institute's infertility clinic will continue during 1977. Improved methods for the diagnosis and treatment of human fertility problems will be applied and evaluated.

Maternal and child health - The Perinatal Biology Center was opened in 1975. Its intensive care nursery and children's ward began functioning in 1976. A program for the care and study of low birth weight infants will evaluate those requiring chronic support and diagnostic studies. The activities in the intensive care nursery will be to determine the dietary composition which will facilitate optimal growth and maturation of the premature infant and the infant

whose placenta was insufficient, resulting in intrauterine growth retardation. Early optimalization of dietary intake in the small infant could have a significant impact on the ultimate potential of the individual. Using a newly devised method, calcium metabolism can now be far more accurately studied in the small infant.

Behavioral scientists will obtain measurements and make observations on the infants being studied in the intensive care nursery in an attempt to accumulate objective data on the effect or lack of effect on the infant participating in the nutritional studies. This type of information is needed because of the high infant morbidity and mortality rates associated with both poor nutritional status and low birth weight infants.

Built around the resources provided by the Perinatal Biology Center, inter-Institute programs relating to infant nutrition and genetic diseases will be developed. A new genetic disease (of glutathione metabolism) has been defined and will be pursued in 1977. Also, research has clearly shown genetic susceptibility to certain carcinogens and mutagens in specific strains of mice. Additional efforts will be directed to detecting such new genetic disorders and defining the specific cause in order that prevention and treatment programs can be devised.

In 1977, the capability to permit the assay of non-radioactive isotopes which are feasible to use in infants and pregnant women will be enhanced. This will permit a number of critical questions to be asked which could not be approached on ethical grounds with radioisotopes. Among these questions will be the attempt to see if cancer and mutational risks can be predicted in humans.

Research will continue to contribute knowledge of the elements of nerve function and the influence of various agents. This work is fundamental to the understanding of and the development of new approaches to mental retardation of several different causes.

An animal model, in the monkey, has been developed for the study of the effect of diabetes in the mother, fetus, and newborn. This system permits the assessment of new approaches to management and treatment of diabetes in pregnancy.

Work will also continue regarding the fundamental mechanism of genetic translation which will be essential to more definitive approaches to the correction of genetic defects. The genetics of forming antibodies which are integral to the body's defense against infection has been totally unclear. This front line defense mechanism is particularly deficient in the small infant. The question has been whether the genetic mechanism concerned with immunity is mutable or fixed. Current studies indicate an enormous diversity in the immune system which arises at least in part from genetic change during the development of the individual.

Epidemiology and Biometry:

The net increase of $12,000 is for $13,000 in mandatory increases such as annualization of pay raise and within-grade increases; offset by a mandatory decrease of $1,000 for one less day of pay in 1977.

Staff in the Epidemiology and Biometry Research Program plan and conduct studies on diseases and conditions relevant to all programs of the Institute, particularly those that are quantitative in character. Clinical trials constitute a major area of activity. In addition, research in statistical methodology is undertaken and consultation to other staff in the Institute is provided.

Infant birth and death certificates will be linked for several states, creating an important epidemiologic resource for analyses of pregnancy outcome and infant mortality. These will include prenatal care, pregnancy history, prematurity and birth weight, on the one hand, and infant mortality by age and cause, on the other. The study of infant mortality will be expanded to investigate counties with extraordinary rates. Studies will be developed to investigate the causes of death in these counties, including nutritional and medical care practices as contributing factors.

In 1976, most one-year examinations of infants treated with phototherapy for bilirubinemia (which is a cause of brain damage) will be completed, and analyses will be possible in 1977 of the potential risks of that procedure. Data management of two other clinical trials, on cystinosis (a congenital disorder) and on H. Influenzae Type B meningitis (the most common etiologic agent in childhood which can cause mental retardation and other health problems) will continue.

Research Management and Program Services:

The net increase of $469,000 consists of a program decrease of $175,000 and a mandatory decrease of $9,000 for one less day of pay in 1977; offset by an increase of $535,000 for mandatory increases, such as annualization of pay raise and within-grade increases and $118,000 for payment to the NIH Management Fund for centrally furnished services.

This activity encompasses (1) the scientific staff associated with the Center for Research for Mothers and Children and the Center for Population Research; (2) the administrative management aspects of grants and contracts; (3) analysis of Institute's programs; (4) research conferences; and (5) program evaluation and general expense assessments.

During 1977, approximately 1,351 grants totalling $88,004,000 will be awarded. In addition, research contracts totalling $19,254,000 will be negotiated and awarded.

The 1977 budget includes $219,000, an increase of $50,000 for the Standard Level User Charge.

Program Management

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
Program Management...	$1,055,000	$1,055,000	$1,113,000	+$58,000
Positions....	49	49	49	--

This activity provides for the overall administration, direction, and coordination of the Institute's programs. It encompasses the Director and his immediate staff concerned with administrative management, program planning and evaluation, and research information dissemination.

During 1977, this activity will continue to provide the necessary professional leadership and technical guidance. The net increase of $58,000 is for mandatory increases of $62,000, such as within-grade increases and annualization of 1976 pay raise; offset by a mandatory decrease of $4,000 for one less day of pay in 1977.

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 and Title X, Section 1004)

1976 Estimate		1977	1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$47,823,000	A/	---	$45,187,000

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. This program is accomplished through the award of research grants, including the Population Research Centers; institutional and individual fellowships; training grants; and research and development contracts.

Accomplishments in 1976: Advances have been made in the development of contraceptive devices for both men and women. Studies centering around contraceptives for men include the evaluation of the combined effects of two steroids on sperm production. Results thus far indicate that this reversible application produces greatly lowered sperm counts, which are incompatible with fertility. Preliminary data have confirmed an increase in congenital malformations among the offspring of women who have been exposed to sex steroids early in pregnancy. Findings have revealed that the risk of prematurity and low birth weight is increased among pregnancies in women who have had prior induced abortions. Behavioral science continues to concern itself with the serious social problems relating to teenage illegitimacy and the motivational factors controlling fertility among couples. Fundamental research continues to support studies in reproductive biology and endocrinology. Of particular interest is the new knowledge on the impact of environmental factors via the brain on reproductive events.

Objectives for 1977: Clinical trials will be carried out to evaluate the safety and efficacy of contraceptives. Research into the development of natural family planning techniques of contraception not dependent upon drugs or devices will be initiated. Research concerned with the safety of oral contraceptives will be continued and the increasingly common contraceptive method of vasectomy will be evaluated. The safety of intrauterine devices (IUDs) will be a continuing project in 1977 and the risks of abortions to subsequent pregnancies will be evaluated. Of particular importance will be the study of teenage illegitimacy, a social problem of increasing concern, and new programs in the economic and environmental consequences of population change. Studies will also be continued on the role of hormones in reproduction.

A/ Title IV, Part E - Indefinite
Title IV, Part I - Legislation pending
Title X, Section 1004 - 1977 Authorization, $60,000,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Research for Mothers and Children (Public Health Service Act, Title IV, Parts E and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$67,107,000	A/	---	$62,071,000

Purpose: The Research for Mothers and Children program encompasses research on the segment of the life span beginning with the moment of conception and extending into adulthood. 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 extra-uterine 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. This program is accomplished through the award of research grants, including Mental Retardation Research Centers and Major Research Programs for Mothers and Infants; institutional and individual fellowships; training grants; and research and development contracts.

Accomplishments in 1976: The pregnancy and infancy program has yielded information important to the sudden infant death syndrome (SIDS) studies. Other accomplishments specifically concern high risk pregnancy and fetal growth retardation as well as continued progress within the areas of maternal diseases and complications and congenital malformations. Continued advances in the growth and development program have been made in the areas of nutrition, learning development, and physiological maturation. Mental retardation research produced accomplishments in genetics, developmental disabilities, treatment of retardation and communication disabilities.

Objectives for 1977: The major area of program expansion will be the Major Research Programs for Mothers and Infants, a new approach developed in 1976 to meet the special health needs of mothers and children. Research on SIDS, prevention or amelioration of health problems contributing to maternal and infant mortality and morbidity, prevention of low birth weight infants, and research into the causes of congenital malformations will be emphasized in the pregnancy and infancy program. Growth and development will concentrate on the areas of nutrition and malnutrition, learning disabilities, the impact of childhood illness on child development, and problems of growth and physiological maturation. The mental retardation program will continue to emphasize research aimed at the prevention or amelioration of mental retardation, particularly through studies on genetics, pregnancy disorders, birth complications, and maternal ill health.

A/ Title IV, Part E - Indefinite
Title IV, Part I - Legislation pending

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Intramural Research and Direct Operations (Public Health Service Act, Title IV, Parts E and I and Title X, Section 1004)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
328	$20,588,000	A/	305	$21,512,000

Purpose: This program comprises (1) the intramural effort, including epidemiology and biometry, in the areas of population and maternal and child health; and (2) the staff responsible for grant and contract programming, review and administration, and the analysis of Institute's programs.

Explanation: The population program includes research in reproductive biology, endocrinology, and ecology. The maternal and child health program includes research concerning all aspects of fetal, infant, and child development, as well as maternal health. This activity also provides the funds for salaries and other operating expenses related to the extramural programs.

Accomplishments in 1976: Population research has provided knowledge about the reproductive processes in male and female. Fertility and infertility research has been enhanced by progress in hormonal studies. The maternal and child health program was enhanced by the new Perinatal Biology Center. Research included: development of a program for the care and study of low birth weight infants; progress in understanding the metabolism of lung surfactant, a deficiency of this metabolic product is associated with respiratory distress syndrome; and continued development of knowledge related to the elements of nerve functions and the influence of various agents important in mental retardation. In epidemiology and biometry, analysis of phototherapy treatment for bilirubinemia should yield significant data on the risks of that treatment. New statistical methods in clinical trials continued to be of interest.

It is estimated that 1,493 grants and 196 research contracts will be funded.

Objectives for 1977: Population research will continue to focus on fertility and infertility problems. Pregnancy complications will be of continued scientific interest and the use of animal models will be helpful in the study of the female reproductive system. With the opening of the Perinatal Biology Center, the maternal and child health's research program will continue to be emphasized. Infant mortality and morbidity caused by pregnancy disorders and diseases will be a concern in 1977. Epidemiology and biometry will link birth and death certificates to provide a resource base for analyses of pregnancy outcome and infant mortality. Bilirubinemia treatment data will by analyzed and statistical information derived from other clinical trials will continue.

It is estimated that 1,351 grants and 192 research contracts will be funded.

A/ Title IV, Part E - Indefinite; Title IV, Part I - Legislation pending; Title X, Section 1004 - 1977 Authorization, $60,000,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

Program Purpose and Accomplishments

Activity: Program Management (Public Health Service Act, Title IV, Parts E and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
49	$1,055,000	A/	49	$1,113,000

Purpose: This activity supports the Director and his immediate staff concerned with administrative management, program planning and evaluation, and research information dissemination.

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 intramural, grant and contract programs are provided under the appropriate budget activity.

Accomplishments in 1976: The staff supported by this activity continued to provide program guidance and administrative management to the Institute's staff, in the furtherance of the Institute's programs to meet its goals.

Objectives for 1977: This activity will continue to provide for the coordination, administration, and direction of the Institute's research programs.

A/ Title IV, Part E - Indefinite
Title IV, Part I - Legislation pending

Transition Quarter Analysis

Budget Authority by Activity

	1976 Estimate		Transition Quarter	
	Pos.	Amount	Pos.	Amount
Population	---	$ 47,823,000	---	$ 6,147,000
Research for mothers and children (formerly child health)	---	67,107,000	---	12,361,000
Intramural research and direct operations	328	20,588,000	328	5,717,000
Standard level user charge		(169,000)		(42,000)
Program management	49	1,055,000	49	266,000
Total obligations	377	136,573,000	377	24,491,000

Explanation

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 years 1975 and 1976.

FEBRUARY 27, 1976.

NATIONAL INSTITUTE ON AGING

WITNESSES

DR. RICHARD C. GREULICH, ACTING DIRECTOR, NATIONAL INSTITUTE ON AGING
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. DeWITT STETTEN, JR., DEPUTY DIRECTOR FOR SCIENCE, NATIONAL INSTITUTES OF HEALTH
DAVID L, CHICCHIRICHI, EXECUTIVE OFFICER, NATIONAL INSTITUTE ON AGING
JAMES R. WEHLING, BUDGET OFFICER, NATIONAL INSTITUTE ON AGING
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT BUTLER, DIRECTOR-DESIGNATE, NIA
WILFORD FORBUSH, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. FLOOD. Now we have the National Institute on Aging with the presentation made by Dr. Richard C. Greulich, the Acting Director of the National Institute on Aging.

I see we have a biographical sketch of you which we will place in the record at this point. We also have a sketch of Dr. Butler, the director designate which we will insert.

[The biographical sketches follow:]

CURRICULUM VITAE OF RICHARD CURTICE GREULICH

Date and place of birth: March 22, 1928; Denver, Colo.
Marital status: Married, 4 children (born 1950, 1954, 1961, 1964).
Business address: Building 31, Room 4B–59, National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20014. Telephone: (301) 496–5345.
Home address: 9621 Dewmar Lane Kensington, Md. 20795. Telephone: (301) 942–3355.
Education:
1944–45: San Jose State College, San Jose. California.
1945–46 and 1948–49: Stanford University, Stanford, California, B.A., Biology.
1949–53: McGill University Montreal, Quebec Ph.D., Anatomy (Biochemistry minor).
Military service: 1946–48: AUS, Private to Sergeant, Artillery (Active Duty). 1948–51: AUS, Sergeant, Artillery (Reserve).
Academic employment:
1949–52: Demonstrator in Histology and Embryology Faculty of Medicine, McGill University, Montreal, Quebec.
1952–53: Teaching Fellow in Anatomy, Faculty of Medicine, McGill University, Montreal, Quebec.
1953–55: Instructor in Anatomy, School of Medicine, University of California, Los Angeles (UCLA).

1955–60: Assistant Professor of Anatomy, School of Medicine, UCLA (on leave 1955–57).

1961–64: Associate Professor of Anatomy, School of Medicine, and Associate Professor of Oral Biology, School of Dentistry, UCLA (on leave 1962–63).

1963–66: Director, Graduate Training Program in Oral Biology, School of Dentistry, UCLA.

1964–66: Professor of Anatomy, School of Medicine, Professor of Oral Biology, School Dentistry, and Chairman, Division of Oral Biology, School of Dentistry, UCLA.

Government Employment:

1966–74—Director of Intramural Research, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland.

1974–75—Staff Director, President's Biomedical Research Panel, Washington, D.C.

1975 to present: Acting Director, National Institute on Aging, NIH.

Related Academic Affiliations:

1955–57—Research Associate, Department of Medical Physics, Karolinska Institutet, Stockholm, Sweden.

1962—Visiting Investigator, Department of Physiology, Royal Veterinary College, University of London, England (six months).

1962–63—Visiting Investigator, Department of Anatomy, McGill University, Montreal, Quebec (six months).

1967–72—Visiting Professor of Anatomy, School of Medicine, University of Virginia, Charlottesville.

Fellowships:

1949–52—United States Atomic Energy Commission Predoctoral Fellow in Biological Science.

1955–57—Bank of America—Giannini Foundation Fellow in Medical Science.

1962–63—NIH Special Research Fellow.

Honors and awards:

1963—International Association for Dental Research Award for Basic Research in Oral Science (inaugural awardee).

1968—Gilmer Lecturer, School of Dentistry, Northwestern University.

1971—Superior Service Award, Department of Health, Education, and Welfare.

1971—Book Dedicatee—"Cellular and Molecular Renewal in the Mammalian Body" (I. L. Cameron and J. D. Thrasher, eds.), Academic Press, New York, xiv + 418 pp.

1973—Election to Membership, Cosmos Club of Washington.

Other Professional Activities:

Consultative:

1959–61—Consultant in Histopathology, Western Biological Laboratories, Culver City, California.

1964–66—Consultant, Skin Research Division, Proctor and Gamble, Inc., Cincinnati, Ohio.

1964–66—Member, Program-Project Committee, National Institute of Dental Research, NIH.

1969–72—Member, International Advisory Research Committee, John F. Fogarty International Center for Advanced Study in the Health Sciences, NIH.

1972—74—Member, Distinguished Scholars Program Advisory Committee, Fogarty International Center, NIH.

Organizational:

1962–68—Member Committee on Educational Affairs, American Association of Anatomists.

1966–70—Member, Awards Committee, International Association for Dental Research.

1968–71—Member, Publication Committee, International Association for Dental Research.

1968–71—Member, Scientific Manpower Commission (representing the American Institute of Biological Sciences).

1970–71—Secretary-Treasurer, Scientific Manpower Commission.

1969–71—Member, Committee on Federal Laboratories (representing the National Institutes of Health).

1971–75—Member, Executive Committee, American Association of Anatomists.

1972–74—Member, Council of the AAAS (representing the International Association for Dental Research).

1969–71—Member, Governing Board, American Institute of Biological Sciences (representing the American Association of Anatomists).
1972–74—Secretary-Treasurer and Executive Board Member, American Institute of Biological Sciences.
Editorial:
1958–65—Co-editor, "International Monograph Series in Oral Biology" (Pergamon Press).
1958–65—Founding Co-editor and Editorial Board Member, "Archives of Oral Biology."
1965 to present: Consulting Editor, "Archives of Oral Biology."
1967 to present: Member, Editorial Advisory Board, "Oral Research Abstracts."
1968–71—Associate Editor, "Journal of Dental Research."
1970–74—Member, Editorial Board, "Journal of Dental Education."
1972 to present: Member, Editorial Advisory Board, "Anatomical Record."
Professional Societies:
American Association of Anatomists.
American Society for Cell Biology.
International Association for Dental Research.
The European Organization for Caries Research (ORCA).
American Association for the Advancement of Science.
American Institute of Biological Sciences.
American Association of Dental Schools.
Sigma Xi.

ROBERT NEIL BUTLER, M.D., DIRECTOR DESIGNATE, NATIONAL INSTITUTE ON AGING, PSYCHIATRIST, PSYCHOANALYST, GERONTOLOGIST, AUTHOR

Birthdate: January 21, 1927.
Birthplace: New York, New York.
Education: B.A., Columbia, 1949. M.D., Columbia, 1953.
Residency: University of California; National Institute of Mental Health; Chestnut Lodge. Diplomate, American Board of Psychiatry and Neurology (P), 1961.
Position: Research Psychiatrist and Gerontologist, The Washington School of Psychiatry, 1610 New Hampshire Avenue, N.W., Washington, D.C. 20009.
Private practice: Psychiatry and psychoanalysis. Group therapy (life crises groups).
Consultative practice: Institutions, agencies, etc. Individual diagnostic consultations. Social, Health, Retirement and Research planning for non-profit institutions (including religious homes for the aging), foundations, public agencies, consulting firms and businesses.
Faculty: Howard University School of Medicine (Associate Clinical Professor); George Washington University School of Medicine (Associate Clinical Professor); The Washington School of Psychiatry; Washington Psychoanalytic Institute.
Consultant: U.S. Senate Special Committee on Aging; National Institute of Mental Health; St. Elizabeths Hospital; Langley Porter Neuropsychiatric Institute (University of California); Center for Law and Social Policy.
Member Boards of Trustees: Group for the Advancement of Psychiatry (GAP); National Council on the Aging; National Caucus on the Black Aged; Washington School of Psychiatry.
Editorial Board: *International Journal of Aging and Human Development; Journal of Geriatric Psychiatry.*
Teaching Experience: University of Chicago; University of Southern California; Catholic University of America.
Research: National Institute of Mental Health, Research Psychiatrist, 1955–1962; The Washington School of Psychiatry, Research Psychiatrist, 1962– . Basic, clinical and community studies. 1. Psychotherapy and Psychology of Middle and Later Life. 2. Follow-up, Human Aging Study of NIMH (11 years). 3. Memoir Study of Persons of Achievement After Middle Life (including major contributors to psychiatry for the American Psychiatric Association). 4. Community Studies.
Public Policy: Action Research, Advocacy, Consultation, Writing, Testimony.
Author: Books—*Human Aging* (with others) (1963; reprinted 1971, 1974); *Aging and Mental Health* (with Myrna I. Lewis), 1973; *Why Survive? Being Old in America*, 1975. Other: Over 100 research and clinical papers in the field

of life cycle, middle age and aging, psychotherapy, confidentiality, drugs, creativity ... as well as book reviews and articles for newspapers and magazines. Regularly featured column, *Public Interest Report* for the *International Journal of Aging and Human Development*. Chapters in *American Handbook of Psychiatry*, the *Comprehensive Textbook of Psychiatry, and Clinical Geriatrics*.

Television: Participant in TV documentaries and co-creator *Lifetime Magazine*, 11974.

Hospital Affiliations: The George Washington University Hospital; The Sibley Memorial Hospital.

Office and Mailing Address: 3815 Huntington Street, N.W., Washington, D.C. 20015.

Telephone: Area Code 202 WOodley 6-4121 and WOodley 6-4199.

Resident of Washington, D.C. since 1958.

Military Service:

1. U.S. Maritime Service—1944–1947; Warrant Officer—Ensign.

2. U.S. Public Health Service, 1955–1962., Senior Surgeon, 1961. Inactive Reserve, 1962–Present.

Other Professional Data: Licenses: State of California, 1955 (April), #C–3152. State of Maryland, 1956, (March). District of Columbia, 1958 (March), #2222.

Organizations:

American Psychiatric Association (Fellow, FAPA, 1963–), 1959– .
Gerontological Society, 1962– .
American Geriatrics Society (Founding Fellow), 1962– .
Washington Psychiatric Society, 1959– .
Washington School of Psychiatry, 1959– .
The Medical Society of the District of Columbia, September 2, 1965– .
Group for the Advancement of Psychiatry (GAP), 1965– .
Forum for Professionals and Executives (Founding Member), 1965– .
Washington Psychoanalytic Society, 1965– .
American Medical Association, 1955–62 (via USPHS).
Southern Medical Association, 1962–65.

Mr. FLOOD. You have some people here you want me to meet, I suppose.

Dr. GREULICH. On my left is our executive officer, David Chicchirichi and to his left our budget officer, Mr. James R. Wehling. On my right is the Director-Designate of the National Institute of Aging, Dr. Robert N. Butler.

Mr. FLOOD. Since you are here, Dr. Butler, if you have any comments to make during the course of these activities, please don't hesitate to do so. We certainly would have no objection to it, if you know what I mean.

I see you have a prepared statement. How do you want to handle it?

Dr. GREULICH. If I may, sir, I would like to read it for the record.

Mr. FLOOD. All right. Go ahead.

Dr. GREULICH. Mr. Chairman and members of the committee, as Acting Director, I am pleased to appear today to present the 1977 budget request for the activities of the National Institute on Aging [NIA], recently created to be the national focus of leadership for research relating to the aging process and the health of the elderly.

ORIENTATION OF AGING RESEARCH

I would like to begin my testimony by providing a brief explanation of what we mean by aging research. Aging is a natural phenomenon which, as far as is known, affects all higher forms of life and perhaps all living things. No matter how aging is defined, its implications for man and his society are profound. Twenty-two million Americans, 10 percent of our population, are now over 65 years old. In 50 more

years, 40 million persons may be that old. Two-thirds of the Federal money spent on health in this country goes for persons over 65. One million people over 65 years of age live in institutions, and a significant proportion of them are incapacitated by a variety of diseases and degenerative conditions. Although the dimensions of the problem are great, they can at least be diminished through continued research.

The obvious need for tangible and immediate improvement in the quality of life for the aged has shifted research away from its exclusive disease orientation, with its study of the sick and institutionalized, to a broader inquiry into normal physiological changes with age, the behavioral constitution of the aged and the social, cultural, and economic environment in which the elderly live. It is this expanded concept of aging research which will dictate the direction of the aging research program in future years, and provides the context for the budget request presented for your consideration.

Before I describe this program, however, allow me to bring to your attention several significant developments that have occurred since the appropriation hearings of last year.

DEVELOPMENT OF THE INSTITUTE

I am happy to report that the NIA is beginning to function as an independent organization within NIH. As you know, a permanent Director has been selected and will be in place by early April. Relevant organizational components of the National Institute of Child Health and Human Development, formerly the focal point for aging research at NIH, were transferred to the new Institute in July 1975. These include the Adult Development and Aging Branch, responsible for extramural grants and contracts, and the intramural research programs of the Gerontology Research Center [GRC], physically located in Baltimore. In addition, a core staff, which will provide direction to and administrative support for the Institute's programs, has now been assembled.

This staff and members of the National Advisory Council on Aging are working hard to complete one of the most important tasks mandated by the Research on Aging Act of 1974, that of developing an aging research plan for the Department of Health, Education, and Welfare. Assisting in this effort are representatives of Federal agencies whose missions are relevant to the field of aging so as to insure their continued input and review at all stages of the plan's development, and ultimately of its implementation. By proceeding in this fashion, we envision the development of a realistic document, one which will allow for constant reassessment and updating as the problems and needs of the elderly change. Design of the plan is on schedule, and it will be forwarded to the Congress by May 31, 1976. Clearly, this plan will serve to identify, even more explicitly, the future research direction of the National Institute on Aging and its relationship to other Federal agencies whose missions also include research relevant to aging or the elderly.

Although 1976 can best be described as a year of planning and organizational development, the ongoing programs of the Institute did produce advances in several areas of research. As a result, many of these promising areas are scheduled for expansion in 1977 and, therefore, warrant further description.

THE AGING IMMUNE SYSTEM

The ability of the body to protect itself against disease—immune function—decreases with age. Discoveries in recent years have confirmed the importance of this loss, while at the same time pointing to the possibility that this process can be delayed by experimental intervention. This year, for example, NIA scientists in the Gerontology Research Center's Laboratory of Cellular and Comparative Physiology in Baltimore showed that certain strains of old mice can be returned to a state of "youthful" immune function by infusion of lymphatic stem cells derived from young donors. Certain chemical reducing agents also seem to rejuvenate the older animal's immune function.

DIET WITH AGING

At the University of California, Los Angeles, a NIA grantee found that by restricting the number of calories or the protein content of an otherwise balanced diet of laboratory mice, he was able to prolong lifespan by 15 to 40 percent, to lower the incidence and growth of spontaneous and transplanted tumors, and to increase resistance to some viral infections. Such regulated animals were shown to possess an immune system which remained or acted younger longer than the immune systems of animals on an unlimited diet. Additional studies to delineate the relationship between diet and age are now in progress.

MENTAL CHANGES WITH AGE

One of the most disturbing aspects of aging is the state of progressive mental deterioration of the elderly called senility. Although generally known by this single name, the condition is probably a composite result of disease-derived changes coupled with more subtle and less well understood deteriorative changes which are intrinsic to the aging brain. Even though this phenomenon is not well understood, there is a method of treating the patients affected by it. For example, NIA scientists found recently that a classical technique used to improve memory—mnemonics—can be taught to elderly people. Once learned, this technique can be used in a variety of ways to improve a person's memory of recent events. This simple method proved to be easily learned by older subjects and was quite effective in helping them store and recall information. This area of study appears to have immediate prospects for application.

HEART FUNCTION IN THE AGED

Previous studies in the Clinical Physiology Branch, GRC, have shown that age is normally associated with an alteration in the relaxation phase of the rhythmic contractions in isolated heart muscle of the rat. Other studies have indicated that a similar alteration in muscle relaxation may also occur in man. This research has now been extended to studies in men participating in the Baltimore longitudinal study, and will continue to be supported in 1977.

SELF-CONTROL OF BLOOD PRESSURE

An estimated 19 million Americans 45 years of age or older are victims of hypertension, more commonly known as high blood pressure.

The magnitude of this problem in middle-age and older adults makes it imperative that more be learned about high blood pressure and the most effective ways to treat it.

Using a technique known as operant conditioning, scientists at GRC have succeeded in teaching patients with hypertension to control their own blood pressures. This technique selectively encourages behavior by rewarding the correct response to certain stimuli.

NEW PROGRAMS IN 1977

The 1977 budget request will allow the Institute to begin programs in several areas that are not adequately addressed by ongoing research efforts and to carry out the mandates of the aging research plan. The present program focuses heavily on the biological process of aging. Although this research is extremely important, the Institute must expand its horizons if the many health problems of the aging are to be solved. Thus, in 1977, the Institute will move to develop adequate resources for future research efforts, and will begin new programs in the clinical, behavioral and societal aspects of aging.

ENHANCED RESOURCES FOR AGING RESEARCH

A primary concern of the NIA is to insure the availability of adequate manpower and animal resources to perform aging research. Because the field of gerontology is not well established in some of our Nation's medical institutions, there is a shortage of adequately trained research manpower. At the same time, the number of young investigators interested in the field of aging, but unable to find funding for their research, is increasing. In an effort to address both of these problems, the Institute has proposed a special research grant program designed to provide funds to young scientists to enable them to pursue independent investigations during the formative stages of their research careers. As many as 75 of these awards could be made in 1977. A further effort to assure adequate research manpower is the award of individual and institutional type fellowships under the authority of the National Research Service Award Act currently proposed for extension. Under this authority, the Institute plans to make 26 new awards in 1977.

One of the major obstacles to the study of the aging process has been the absence of suitable laboratory animals on which scientists could either perform their experiments or systematically observe the aging process. Until recently, investigators throughout the country were unable to acquire supplies of shorter-lived species of common laboratory animals, notably rats and mice, in a fashion which would provide adequate numbers of all age levels. The reasons for this difficulty were the tremendous expense involved in their production and the poor health status of the old animals that were available. As an example of the cost of these animals, I would like to point out that a 26-month-old rat produced by a contractor costs $80 and that a kennel maintained beagle, 10 to 12 years old, costs $1,500.

A significant contribution by NIA to the advancement of basic studies of the aging process is the establishment and maintenance, through contract, of a germ-free colony laboratory of rats and mice, of known

genealogy, at different ages, and in numbers sufficient for aging research. However, it is imperative that action be taken now to insure a growing supply of animals for future research. The NIA has, therefore, requested funds in this budget for assuring adequate numbers of high quality animals for research supported extramurally under grants and intramurally at the Gerontology Research Center in Baltimore.

PROJECTED RESEARCH ON CLINICAL, BEHAVIORAL AND SOCIETAL ASPECTS OF AGING

Several new programs are planned in the clinical, behavioral, and societal aspects of aging. For example, the GRC began a longitudinal study of aging in 1958, which now has 650 men actively participating. Data produced by this study will not have validity with respect to the general population without a female component. Therefore, the NIA will prepare in 1977 for the addition of women to this study with the intention of implementing the program in 1978.

One important area of concern is the finding that certain classes of therapeutic drugs elicit unexpected responses when administered to elderly patients. Such paradoxical reactions are frequently opposite to the response which would normally be anticipated. In view of the frequency of these occurrences and the growing number of elderly patients receiving drugs, NIA will begin in 1977 a systematic research effort to determine the cause of change in drug sensitivity and response as a function of increasing patient age.

To date a limited number of studies supported by the Institute have dealt with individual adjustments to the problems of aging, but little is known about the relationship between social factors and the health of the aged. For example, a major problem of the elderly is social, economic, and physical dependency. In order for the NIA to help keep elderly people independent and functioning members of society it must conduct research on such factors as the effect of mandatory retirement, the problem of transportation to community and medical care facilities, and the stigma attached to old age.

The prevention or amelioration of the debilitating effects of old age is another area of concern to the NIA. Research findings to date indicate that changes in behavior early in life may have the effect of warding off some of the adverse consequences of the normal aging process. For example, the longitudinal study conducted by the Gerontology Research Center suggests that exercise may lead to a longer life. There are, of course, numerous other factors that require study in order to make similar determinations concerning current behavior and subsequent health. The NIA plans several studies in this area during 1977.

CONCLUSION

In conclusion, the 1977 budget allows the NIA to begin full implementation of the mandate contained in the Research on Aging Act of 1974 by expanding existing programs and beginning several new ones. Mr. Chairman, the 1977 budget request for the National Institute on Aging is $26,220,000, an increase of $6,832,000 over the 1976 comparable appropriation of $19,388,000.

Thank you, and I would be happy to reply to questions.

COST OF ANIMALS FOR AGING RESEARCH

Mr. FLOOD. It might not be the best way to begin, Doctor, but we are talking about research. You mention that the 26-month-old rat produced by a contractor costs $80.

I am afraid in the record that is going to upset a lot of people when we are spending so much elsewhere in our budget on rodent control, Federal, State, and local. The fact is the rats they are concerned about in these programs, are diseased or of such a nature they couldn't possibly be utilized for research activity. Would that be true?

Dr. GREULICH. That is quite correct. Indeed, the animals that we are paying that kind of money for are derived by caeserean section from the outset so they don't even pass through the birth canal.

Mr. FLOOD. You can see why I wanted at the very beginning to clear that one up.

Dr. GREULICH. Yes.

THE AGING RESEARCH PLAN

Mr. FLOOD. You mentioned you intend to submit a plan for aging research to the Congress on May 31 this year. Was the 1977 budget developed around the research priorities that are to be contained in that aging research plan?

Dr. GREULICH. To the extent that the plan speaks to the Institute on Aging as opposed to the other agencies within the Department of Health, Education, and Welfare, which also have mandates relating to the aging or the aged, the answer is certainly "Yes."

COORDINATION OF AGING RESEARCH ACTIVITIES

Mr. FLOOD. Doctor, when Dr. Kretchmer was here and testified I remember we asked him about a formal plan that was going to be developed to coordinate research between the Child Health and Human Development and Aging Institutes and let me quote what he said: "I wish I had one at the moment."

And he also told us that he would send up a copy of the coordinating plan to the committee when it was completed. Do you have such a plan at this time? In your statement you were talking about a plan. Are we talking about the same thing?

Dr. GREULICH. I can't speak for Dr. Kretchmer in that regard.

Mr. FLOOD. Do you have such a plan?

Dr. GREULICH. The NICHD, in cooperation with the NIA, has developed such a plan. I believe that if it is not in your hands yet it will be in your hands very shortly.

Moreover, let me assure you there has been ongoing coordination at the administrative level between the two Institutes ever since the NIA was established.

Mr. FLOOD. It is not generally understood that some of these questions on the aging will come from studies of infancy and childhood. That coordination is essential.

Dr. GREULICH. We certainly subscribe to that.

Mr. FLOOD. Tell that to the first fellow you meet out in the hall here and he will think there is something the matter with you. How we are going to stress that I am not clear, but we know what you mean here.

EXPANSION OF RESEARCH ON SENILE DEMENTIA

As you know, this country has over a million persons in nursing homes. Many of them are incapacitated or have senile dementia. Do you plan to expand research on those diseases, particularly on this disease of senile dementia?

Dr. GREULICH. In direct response to your question on senile dementia, we certainly do hope to be able to expand our efforts in this area in concert with ongoing efforts of other Institutes at the National Institutes of Health and with the National Institute of Mental Health, all of which have programs bearing on senility and senile dementia.

Mr. FLOOD. Of all the medical/technical terms, that is a phrase that the public is pretty well aware of, the term "senile dementia." They have been for years. You hear that said in the most unusual places, so there you have a public acceptance and any indication of research in that area would be widely understood.

Dr. GREULICH. Yes.

COORDINATION WITH THE NATIONAL INSTITUTE OF MENTAL HEALTH

Mr. FLOOD. This appears to be an area that the National Institute of Mental Health will also, I take it for granted, be interested in researching. How do you plan to work with NIMH on that?

Dr. GREULICH. The National Institute of Mental Health has recently established a Center for Studies of the Mental Health of the Aged. We are already in close contact with the individuals who are concerned with the administration of that enterprise.

I would go on, however, to mention that part and parcel of the development of the Secretary's research plan on aging will be recommendations as to how best to create consistent and rational techniques of coordination, so that we do things in a complementary fashion.

MAJOR RESEARCH AREAS

Mr. FLOOD. Will you identify for the committee the major research areas that are going to be supported by this budget and tell us why you selected those areas. Did you just pick them out of the air, or why did you select those areas? What are they and why?

Dr. GREULICH. We have two presentations of this kind of information. Perhaps it would be best for me to state now that most of the programs that we are proposing for 1977 are expansions of pre-existing programs. More effort on behalf of the public is obviously needed.

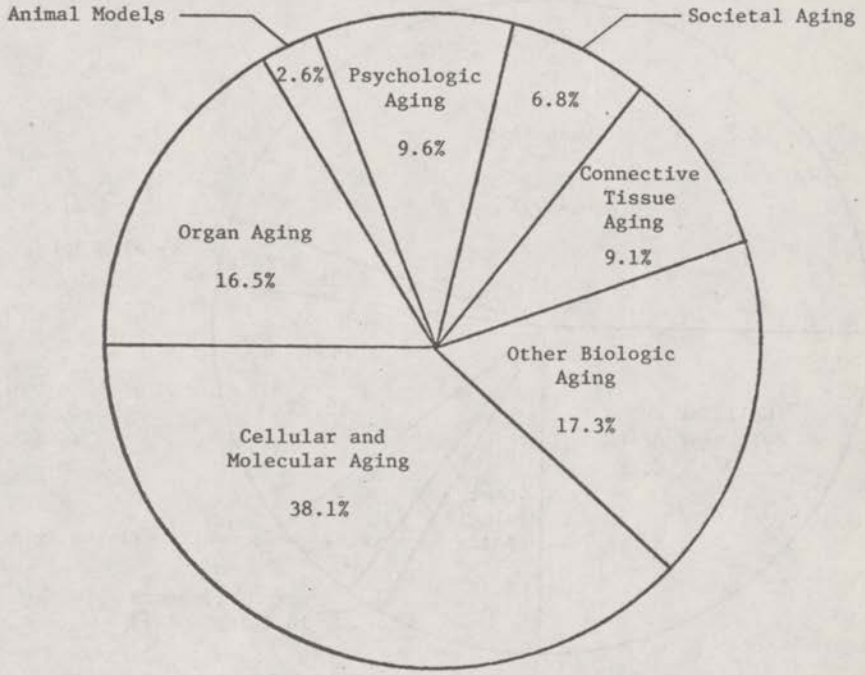
We are moving in the direction of trying to establish a better balance among the major segments of our effort which are biomedical research, clinical research, behavioral research, and social research. We have a chart which we would be happy to submit for the record to show the percentage of effort in these four areas.

Mr. FLOOD. All right, do that.

[The information follows:]

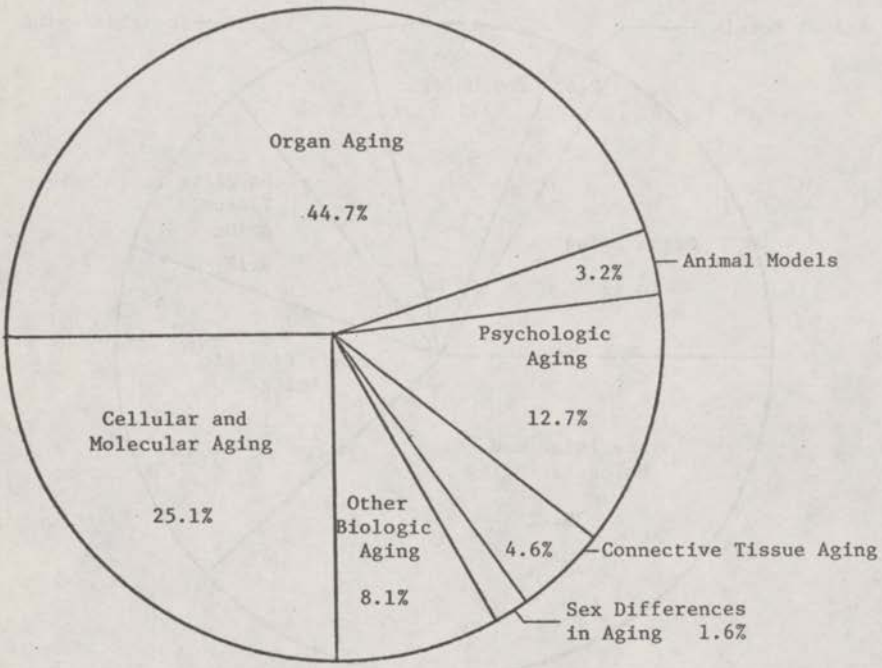
NATIONAL INSTITUTE ON AGING

Percentage Distribution of FY 1975 Obligations
for Extramural Research by Scientific Category



NATIONAL INSTITUTE ON AGING

Percentage Distribution of FY 1975 Obligations
for Intramural, Laboratory, and Clinical Research
by Scientific Category



AVAILABILITY OF RESOURCES

Mr. FLOOD. You are continuing what you are doing and then you have these other programs throughout the Department.

Dr. GREULICH. That is right.

Mr. FLOOD. Are there any areas that really appear to have potential for addressing these many problems of the elderly which are not going to receive any funding under this budget because of limited resources?

Dr. GREULICH. I think a fair answer to that question from a dollar standpoint is that nothing is going to be shortchanged.

OPERANT CONDITIONING

Mr. FLOOD. You mentioned biofeedback techniques to help the elderly, control of blood pressure, and so on. That is quite a phrase. Can you tell us more about that technique and its impact maybe on other diseases affecting the elderly?

Dr. GREULICH. I would be happy to describe the use of that approach.

This operant training or biofeedback training has been explored in a number of situations. Last year I believe Dr. Kretchmer reported to you on its application to the problem of fecal incontinence, a very troublesome and, unfortunately, highly common problem in older people. It has been established under carefully controlled clinical situations that patients can be taught to voluntarily control the functioning of their bowels.

Mr. FLOOD. How long will it take to teach someone like that?

Dr. GREULICH. It depends on the patient. It is a highly individual thing. One of the other points concerning an important research aspect, quite aside from the potential for public benefit, is that the psychologists themselves are trying to learn why it works. They really do not know what the processes are that go on within an individual that enable him to control blood pressure, heart rate, bowel function, and so forth. It is a dual research undertaking that will payoff not only to the body of science on the one hand but most importantly to the people on the other.

CURRENT APPLICATIONS OF OPERANT CONDITIONING

Mr. FLOOD. Are you talking only of blood pressure?

Dr. GREULICH. No.

Mr. FLOOD. Why I was concerned was since you are doing that on blood pressure, could there be any other diseases affecting the elderly that would be covered as well?

Dr. GREULICH. I would not refer to these as diseases as much as abnormal conditions. Hypertension, for example, or abnormal heart rhythms, and occurrences of this sort may or may not of themselves constitute disease.

There may be other extensions. At the moment with the limited manpower resources at hand we are focusing on the control of blood pressure and the heart rate.

Mr. FLOOD. Can an elderly person continue to use this technique without that feedback machine?

Dr. GREULICH. The relatively few people who have been trained thus far with respect to blood pressure have been followed in their own home environment and indeed they can.

It is like learning to ride a bicycle I suppose; once learned it is very difficult to forget.

FUTURE APPLICATIONS OF OPERANT CONDITIONING

Mr. FLOOD. Do you see that this is going to have a very wide practical application among the elderly in the future?

Dr. GREULICH. In institutional settings it might very well have. One would have to recall, however, that there is a very intensive learning experience that is involved here. The situation requires teams of teachers, almost one on one with the patients.

Mr. FLOOD. When I say how long does it take and you reply that depends on the individual. There is no set time, 3 months, 90 days, anything like that?

Dr. GREULICH. For the most part we have had very great success in a period under 6 weeks.

Mr. FLOOD. That is what I was trying to get at. Within reason under 6 weeks?

Dr. GREULICH. Yes, sir.

COOPERATION WITH THE HEART INSTITUTE

Mr. FLOOD. Since you are using this biofeedback technique for controlling the blood pressure, do you intend to conduct a collaborate research program with the Heart Institute people since they are so concerned with hypertension affecting all age groups, not just the elderly?

Dr. GREULICH. That has not yet been discussed, but is an obvious potential extension.

Mr. FLOOD. They are dealing with the whole spectrum; I would think so.

FECAL INCONTINENCE

Dr. GREULICH. May I comment on one other aspect of the operant conditioning, and that has to do with control of the bowel, which I mentioned briefly a moment ago.

We are moving into a collaborative program with the Veterans' Administration to see how efficacious that process really is under broader institutional settings and under somewhat different clinical conditions.

Mr. FLOOD. Are you just dealing with males mostly—not altogether, but 99 percent?

Dr. GREULICH. There are virtually no biological differences in bowel function between males and females.

PARADOXICAL DRUG REACTIONS

Mr. FLOOD. Last year we talked about identifying the correct dosage of drugs given to the elderly in order to equal the lower metabolic rates they have. Would you be supporting independent pharmacological studies in this area or do you intend to again collaborate with

the National Institute of General Medical Sciences because of their very extensive pharmacological capability?

Dr. GREULICH. We have been in close contact with officials of NIGMS. We also propose to indicate our interest in this area to the scientific community and elicit grant applications from them.

Mr. FLOOD. What drugs are you currently evaluating? What have you learned about your work in that area?

EVALUATION OF ALCOHOL AS A DRUG

Dr. GREULICH. Most recently the only drug to which I can direct your attention is alcohol, which is one that you may not want to think of as a drug necessarily but it is.

Mr. FLOOD. There is no public acceptance of the decision not too long ago that alcohol is a drug. If you walk out in this hall and talk to the first fellow out there and you tell him that, he will think you are drinking. That alcohol is a drug, I don't know how we can stress that. There is a total lack of public awareness of that.

But more specifically how do you intend to inform the practicing physicians that they should prescribe medicine differently for the elderly?

Dr. GREULICH. That is a hard question to reply to.

Mr. FLOOD. I have had more argument with GP's about that one. I have had them actually say, "Well, why." I say, "Don't ask me why. I am asking you." And there we are in a circle.

Dr. GREULICH. One does find in most of the literature that accompanies drugs or in the textbooks that relate to drugs that there are shortages of information about what indeed is an appropriate level of medication for an older person.

Mr. FLOOD. This is so. I have seen some of those information sheets that have italicized paragraphs on them.

Dr. GREULICH. There is an increasing awareness. However, I do not mean to infer that we are going to depend on the pharmaceutical houses alone for the dissemination of this kind of information.

Mr. FLOOD. How do you inform the practicing physicians?

Dr. GREULICH. As information is accumulated we would propose to disseminate it through the channels that are already in existence within the framework of the National Institutes of Health. We also plan to use short, snappy, impacting kinds of communications that could be mailed to practicing physicians. These could also be made available to the public through a number of channels.

REDUCTIONS FOR RESEARCH TRAINING

Mr. FLOOD. Despite everything you said, the 1977 budget proposes a slight reduction, for training manpower for the field of aging research. We had the impression there was a considerable shortage of manpower in this field.

Did that shortage disappear overnight or what?

Dr. GREULICH. Quite the contrary; it is not disappearing, but I would comment that the reduction that appears in this budget is in part an accident of time.

The old training authorities are being phased out. Our previous training was done under section 301 of the Public Health Service

Act. We are in the process of phasing out these awards and phasing in the National Research Service Award Act.

Mr. FLOOD. Why didn't you allocate more of your additional resources to training? You have an overall increase here of 52 percent and yet you are reducing training. How can we understand the process, whatever the process was, that led you to, under all the circumstances, reduce training, with a 52 percent plus in there?

Dr. GREULICH. We will have the opportunity to make 13 additional fellowship awards during the coming year. The decreases are largely those of the phaseout of the old training authority, as I said before.

Dr. FREDRICKSON. I think there will be a net decrease.

Mr. FLOOD. Yes.

TRAINING IN GERIATRIC CARE

In talking to medical administrators in the specialty fields, we understand that most of our medical schools and nursing schools rarely require students to be exposed to nursing homes or even to the elderly population in order to gain some kind of experience in the principles of geriatric care. That seems to be traditionally a practice. Well, what role will your Institute play in changing that situation? What should the Health Resources Administration be doing to correct that very obvious situation?

What is the Institute doing about this?

Dr. GREULICH. We are very concerned about this solution for it. As you probably realize, the medical schools of this country have gone through many curricula changes over the past 15 years, from which I do not think they have entirely recovered. Further changes, therefore, need to be approached with caution.

Mr. FLOOD. In my congressional district the average age is perhaps 12 to 13 years above the national average. I talk to a lot of medical students in my area. They are concerned about that. They know about that fact. They told me they don't go to nursing homes. They have to take extra lecture courses, for which they get no credit, in geriatrics someplace at 4 p.m. or something.

Dr. FREDRICKSON. Mr. Chairman, may I add a note to your question before? I think there is a real difficulty in getting a commitment from the professional community to the real problems of the aging—a recognition that these are real problems, as real as those that just occur in adults or in children. Getting people to pay attention to them is very important. I think the establishment of this Institute and the creation of a vigorous effort is going to give tremendous identity to the field.

It will have a very important influence in attracting people into the field. That we will be creating research opportunities and can show that the knowledge can be expanded and usefully applied will have a very positive influence on recruitment.

Mr. FLOOD. I think you are absolutely right.

MEETING LEGISLATIVE GOALS

Doctor, from what I have read and from what a lot of people tell me the answer to the problems of the elderly isn't as simple as funding more behavioral or biomedical research programs. A complete reevaluation is needed of all the programs of the aging in order to see

whether we have fallen short of our legislative goals. Have we fallen short of our legislative goals?

Do you agree with that? Why have we fallen short of the legislative goals in this area?

Dr. GREULICH. I couldn't agree with you more and it would seem to me that this feeling on your part and on the part of others led to the creation of the National Institute on Aging. Consequently we do have a mandate to do something about it.

May I return to the issue of curricula of universities and medical schools long enough to point out that we do propose to contract with the American Geriatric Society to study what is feasible within the framework of existing medical education in regard to curriculum changes. The next step is to identify particular institutions where such programs could be tried out on an experimental basis, such that medical students would indeed get better exposure to the problems of the elderly.

SUICIDE AMONG THE ELDERLY

Mr. FLOOD. We understand that one out of every four suicides in this country is committed by people over the age of 65 years.

Dr. GREULICH. Correct.

Mr. FLOOD. I am sure that isn't generally known. What do you know about the factors that cause this to happen? Are you conducting any research in this area? It would occur to me that is quite a thing.

Dr. GREULICH. At the moment I don't believe that we are supporting any research in this area.

Mr. FLOOD. Once you bring up the question everybody understands.

Dr. BUTLER. It is critical.

Dr. GREULICH. No question.

NURSING HOME CARE

Mr. FLOOD. Everybody has been concerned for quite a long time now about the quality of care in nursing homes. What do you recommend we do about that situation? What can we do to make them function better?

I didn't say what can you do. What can we do, all of us?

Dr. GREULICH. It seems very clear to me, and this is a personal feeling, in addition to the kinds of survey information which are now in the process of being accumulated by the Office of Nursing Home Affairs, that there are very great needs for research either under the auspices of NIA or one of the other Federal agencies, to determine the kinds of alternatives to institutionalization that could be introduced and implemented. Included among these is home care, which, according to present-day thinking seems to be the most viable option. This research could result in developing a greater awareness of, and greater skills for, keeping older people within their own home environment.

These questions still require research and followup evaluation.

PROCUREMENT OF RESEARCH ANIMALS

Mr. FLOOD. Mr. Michel.

Mr. MICHEL. Thank you, Mr. Chairman.

Let me begin where the chairman began on this animal business just for a moment because of that tremendous cost, and all the other

Institutes or all NIH's activities depend, in no small measure, too, on rats or whatever animals are used.

Is there a sufficient need for NIH to have its own production capacity for these research animals? Has anybody done a study as to whether or not it would be more reasonable for us to do it? Far be it from this free-enterpriser to have Government encroach upon a legitimate private enterprise where that can be done more cheaply on the outside, and I guess I am really asking you point blank has a study been made? Do we know whether or not we are getting it done cheaper on the outside than we could do it inhouse?

Dr. FREDRICKSON. I don't think that we are but there are certain circumstances that have dictated increasing our reliance upon contractors in recent years—primarily the ceiling on personnel. We cannot do this inhouse with the current resources that we have. We have done a study, of course, on comparative costs and could provide you material on that.

Mr. MICHEL. I wish you would and then, if you can, provide any conclusions you have reached, which I assume you have.

Dr. FREDRICKSON. Yes, we have.

[The information follows:]

COST OF ANIMALS FOR RESEARCH

NIH is currently using large numbers of contract-produced animals in its research programs. Small numbers of research animals are also produced in government facilities. There is a wide range of animal species used in biomedical research. Within some of the species, there are a number of specialized strains and stocks. For example, NIH is the source of 150 different strains of rodents with unique characteristics vital to biomedical research. These include hypertension, diabetes, and spontaneous appearance of cancer. Much highly specialized animal work is performed in our facilities with our personnel because these animals are not available elsewhere. We are continuously seeking or developing contract sources for the production of these and other research animals. This enables us to use our space at Bethesda in a most effective manner.

The contract mechanism is viewed as a major source of supply for many of the animals used in NIH research programs. However, factors in addition to costs must be considered before decisions on the most appropriate supply source are made. Contractors are capable of economically producing those animals used in large numbers. Highly specialized animals used in small numbers often cannot be economically produced commercially. We do maintain small production colonies for specific purposes.

Total reliance on contract animals could lead to serious problems in maintaining the integrity of the research projects at NIH. Major disease outbreaks in contractors' facilities could have devastating results on biomedical research if no other sources of supply were available. NIH maintains small production colonies of many of those animals to offset such occurrences. Not only would the scientists be supplied during this period, but the contractor would be provided new breeding stock to reestablish his production.

The maintenance of small production colonies at NIH also provides us with a standard by which potential contractor cost proposals and end products can be compared. For instance, NIH foxhound breeding experience was responsible for a 75-percent reduction in the contractor's original proposal for the supply of these animals.

NIH continues to be active in the development of breeding contracts to meet current demand. In highly specialized areas requiring small numbers of animals, NIH supplies its contractors with pedigreed breeding stocks and purchases the progeny. Contracting permits us to focus our inhouse efforts only on developing those animals with special characteristics such as pedigree, history, age, and known blood groups not available commercially. This enables us to assure the genetic integrity of animals while continuing to increase private industry's share of the research animal market.

Mr. MICHEL. And, if nothing else, if somebody has a monopoly on this thing and the price keeps getting jacked up, eventually I would be put to the wall and would say, "Look, we are going to do it ourselves."

That is a striking figure when you talk about a 26-month-old rat for $80 or that 10- or 12-year-old beagle, and I guess if you are researching in aging you don't want any pups, or if you do, only for comparison of young and old.

Dr. GREULICH. Correct.

POSITIONS FOR THE AGING INSTITUTE

Mr. MICHEL. How many people do you currently have on board?

Dr. GREULICH. 176.

Mr. MICHEL. How many do you expect to have in 1977?

Dr. GREULICH. Our budgeted positions are reduced from 193 in fiscal year 1976 to 173 requested in the 1977 President's budget. The 1977 level is 173 positions whereas we currently have 176 on board.

NEW AND EXPANDED PROGRAMS

Mr. MICHEL. Just about the same. You do have an increase of about $5.7 million for 75 new research grants.

Dr. GREULICH. That is correct.

Mr. MICHEL. How do you plan to allocate these grants among your programs?

Dr. GREULICH. As I mentioned previously, we are planning to stimulate more research in the social sciences for which we are projecting an increase of 18 grants in the amount of $1 million. We are also enhancing behavioral science research by $500,000 and nine grants.

Also, we are supporting very little clinical research at the moment. Clinical research on aging is difficult and very hard to get people to do. We think that with the availability of research funds those people who are available will respond. The planned increase is $500,000 and nine new grants.

CHALLENGES OF AGING RESEARCH

Mr. MICHEL. Why do you say it is hard to get people to do this? You have just said in your testimony we have—how many?—20 million people over 65, and we will double that figure conceivably within a relatively short span of time. Wouldn't your researchers, bright people, look to this and say there is one area where the demand is going to be increased, not declining?

Dr. GREULICH. There is no question about the demand. I can only infer that this represents sort of a melding of two situations. One is the lack of effort and attention to the specific needs of older people as young physicians get their medical education.

Second, I think there is a need to make aging research more attractive. I mentioned in my statement that, in addition to the programs in categorical areas of research, we also wish to try to develop as many as 75 special grants for newly trained investigators who would com-

pete for modest sums for doing research. Potentially, a portion of these individuals would be clinically trained.

This new program is an attempt to increase, on the one hand, the number of people doing research related to aging and the aged, and also to get bright young people who might avail themselves of other career options, interested in the aging process. It is a technique which has worked successfully in other Institutes and we have every reason to believe it will be successful with us.

We are therefore planning approaches designed to overcome in time the personnel shortages to which you allude.

Mr. MICHEL. You spoke in your testimony and statement of an infusion of lymphatic stem cells. I don't know if we can equate this with youth serum or what, but conceivably there could be some excitement in this area if some researchers came up with a magic tonic for extension of life.

Dr. GREULICH. Correct.

The immunological aspects of aging appear to be as dramatic as any in terms of possibilities for asking good research questions. I would predict that a large number of the people will submit research grant proposals on some aspect of the changes in immunity as their primary theme.

DIET AND AGING

Mr. MICHEL. You touched on the topic of diet in the process of aging. Do we know anything significant yet about that by way of accomplishment or recognition?

Dr. GREULICH. It is a finding which in some ways is a reproduction of work that was done many years ago by a gentleman named Clive McKay who showed that caloric restriction in young animals alone would extend their life expectancy.

Mr. MICHEL. Do you mean restriction?

Dr. GREULICH. Restriction. You don't starve them to death. You just control their intake. The interesting and more revealing aspect of the point I make in my opening statement was that this seems to be somehow reflected in the immune function of the animal.

In other words, the caloric and protein restriction was known to have some favorable impact on life expectancy in animals but the mechanism of that was not understood. This still doesn't tell us all the answers about the mechanism but it does offer a very interesting lead to explain it.

To directly answer your question, very little is known about the nutritional needs of older people and I would hope that as the National Institute on Aging begins to expand and becomes more solidly based that this area will be taken most seriously.

THE BALTIMORE LONGITUDINAL STUDY

Mr. MICHEL. What is this Baltimore longitudinal study?

Dr. GREULICH. This is a group of some 650 male volunteers, ranging in age from 20 to 93, some of whom have been a part of an ongoing examination for upward now of 16 years. In fact, the gentleman sitting on my left is one of the volunteers. The reason for this kind of

study is that it is difficult to appreciate all of the nuances of the aging process simply by comparing a group of 85-year-old people with a group of 40-year-old people.

There are all sorts of different life experiences that are totally incomparable between those two groups. You can't simply say that here is something that seems to go on in an 85-year-old and here is something else in a 45-year-old; therefore, the 45-year-old will look like the 85-year-old when he gets that old.

What really needs to be looked at is how does an individual, or in this case a group of individuals, change physically, mentally, and so on as they progress and how does senescence relate to the quality and duration of their life expectancy.

HYPERTENSION IN THE AGED

Mr. MICHEL. What are you doing in the hypertension field, if anything?

Dr. GREULICH. We have relatively small efforts in the hypertension field. This field is obviously much more the responsibility of the Heart Institute. I have mentioned the behavioral conditioning project earlier.

THE SPECIAL RESEARCH GRANT PROGRAM

Mr. MICHEL. You make reference in your statement to, "a special research program designed to provide funds to young scientists to enable them to pursue independent investigations during the formative stages of their research years."

Does this represent really a legitimate research program, or just kind of a carrot out there dangling to attract or subsidize research scientists?

Dr. GREULICH. I think it is a very legitimate means of expanding the community of researchers who are focused on a particular subject area, in this case aging. A young man who finishes medical school or finishes a doctoral degree in one or another of the basic disciplines may not have finalized his choice of career or scientific field.

The availability of small startup research funds, which is what this is, is an opportunity not only to take advantage of their training and abilities but also to influence their choice of aging as a field in which they want to work.

Mr. MICHEL. What do these grants average?

Dr. GREULICH. The overall total cost is probably in the nature of $14,000. This level of support gives us an opportunity to test at a rather modest cost whether this person really has anything to offer to the aging research community.

In a sense it is a risk capital investment, but many very good things have come out of this method.

Mr. MICHEL. How much overall are you allocating to this?

Dr. GREULICH. We are allocating approximately a million dollars for this purpose with the view of supporting as many as 70 to 75 people.

Mr. MICHEL. That is all, Mr. Chairman.

Thank you.

POSITIONS FOR PROGRAM MANAGEMENT

Mr. CONTE. On page 2 of the opening statement, you mention a core staff. What is the size and function of this staff?

Dr. GREULICH. The core staff referred to in the opening statement is located in the Office of the Director, which provides overall control of, and direction for, the Institute's programs. In the fiscal year 1976 appropriation bill, 25 budgeted positions are authorized and 12 of these positions have been filled. The 1977 President's budget proposes 5 budgeted positions for this function, a decrease of 20 from the 1976 authorized level.

FISCAL YEAR 1976 ACTIVITIES

Mr. CONTE. How much of the Institute's time was spent on planning and organizational development as opposed to research last year?

Dr. GREULICH. Research continued without interruption during and subsequent to the transfer of the research programs of the Gerontology Research Center in Baltimore and the extramural grant and contract activities managed by the Adult Development and Aging Branch from the National Institute of Child Health and Human Development to the National Institute on Aging. The 150 members of GRC's staff were fully occupied with ongoing research activities relating to the aging process. Likewise, our science administrators in the Adult Development and Aging Branch continued their program management functions in support of research grants and contracts in aging. The point in my opening statement regarding planning reflects the priority given to the development of the Secretary's aging research plan by the Institute's administrative staff. While this process represents a substantial effort it in no way interfered with the advancement of our research activities.

DIET AND IMMUNE RESPONSE

Mr. CONTE. Can you tell us a little more about your investigation into diet-immune system connection which you mentioned in the opening statement?

Dr. GREULICH. The investigation of the diet-immune system connection refers to a study done by a National Institute on Aging grantee at the University of California, Los Angeles, utilizing mice.

The research protocol was based on studies conducted approximately 25 years ago. With modifications to the earlier approach, the investigator made his preliminary observations that restriction of caloric intake led to a more "youthful" responding immune system. It must be stressed that these are preliminary observations and that additional studies to delineate the relationship between diet and age are now in progress.

EFFORTS IN HYPERTENSION

Mr. CONTE. Could you estimate or provide for the record the amount you spend on hypertension research?

Dr. GREULICH. As you know, the Heart Institute has primary responsibility for hypertension research and, therefore, our efforts in this area are relatively small. We do spend approximately $65,000 on a study that uses operant conditioning to bring about such changes as lower blood pressure. We also have two grants in the hypertension area amounting to approximately $45,000.

AGING RESEARCH PERSONNEL

Mr. CONTE. What is the current manpower situation in aging research? Where are the shortages critical?

Dr. GREULICH. While there is a highly competent and dedicated community of research expertise currently focusing on problems related to the aging and the aged, it is manifestly clear that the size of this community is not presently commensurate with national demands. For that reason, the National Institute on Aging proposes to utilize training authorities under the National Research Services Act, as well as the special research grants program, which I mentioned in my opening statement, to expand the number of researchers in the field. We shall also give greater consideration to the numbers of people to whom we provide fellowship or grant support in terms of their area of interest. More specifically, we are concerned with research in clinical, social, and behavioral aspects of aging. We believe that judicious application of our available training and grant moneys can result in achieving more interest in these areas, and thereby a better balance of effort.

SPECIAL RESEARCH GRANT PROGRAM

Mr. CONTE. Do you plan to expand the special research grant program mentioned on page 5 of the opening statement, beyond the 75 proposed for 1977?

Dr. GREULICH. Because 1977 will be the first year for this program, it is difficult to say at this point in time whether an expansion beyond the 1977 level is warranted. The National Institute on Aging will want the opportunity to assess the interest shown in the program, the quality of research supported, and the effectiveness of attracting bright investigators into the aging field before it proposes an expansion of this effort.

PHYSICAL ACTIVITY AND LIFE EXPECTANCY

Mr. CONTE. What evidence is there to connect exercise at earlier stages of life with longer life spans?

Dr. GREULICH. Before I answer your question directly, let me point out that it has not been proven that there is a positive relationship between regular physical activity throughout life and a longer life expectancy. There have been no prospective studies, and there are none in progress, that relate the effect of exercise in early childhood or in adolescence to life expectancy. Retrospective studies of college athletes and life expectancy have been done but are inconclusive at best.

There are tentative data, however, that are coming out of our longitudinal study which indicate a relationship between exercise in one's later years and life expectancy. These data are based, at present, on a small sample and are not definitive. The tentative findings are interesting and we plan to further investigate this question. It is one of the many social factors that need to be studied in order to determine the appropriate role they play.

RESEARCH ANIMAL FACILITIES

Mr. CONTE. What will be the cost of upgrading the animal facilities?

Dr. GREULICH. Our current estimates indicate that upgrading the animal facilities at the Gerontology Research Center in Baltimore will

cost $250,000. This amount will provide for renovations to the animal quarters and for modern caging, as well as improved animal husbandry. These improvements are important to ensure the reliability of data obtained in future experiments utilizing these animals.

OPERANT CONDITIONING

Mr. CONTE. What recent accomplishments have been made in the area of behavioral training procedures and biofeedback?

Dr. GREULICH. Operant conditioning or biofeedback training is a process which selectively encourages behavior by rewarding the correct response to certain stimuli. Through an intensive learning experience, usually within a period of 6 weeks, patients have been taught to control their own blood pressures, heart rates, or bowel functions. One point that should be emphasized is that an important research aspect of biofeedback, quite aside from the potential for yield to the public, is that the psychologists themselves are trying to learn why it works. While these studies continue, the National Institute on Aging is arranging a collaborative program with the Veterans' Administration to see how efficacious it is in the control of bowel function under somewhat broader institutional circumstances.

COORDINATING IMMUNE RESEARCH

Mr. CONTE. How does you work on the immune system conflict or overlap that being done by the Institute of General Medical Sciences?

Dr. GREUDICH. Our work on the immune system does not conflict or overlap with other related research in the other Institutes at the National Institutes of Health, but rather complements it. The mechanism at the National Institutes of Health which protects against overlap is the method of assigning research grants to each of the Institutes for possible funding. Upon receipt of an application in which more than one Institute has an interest, it is assigned to each of these Institutes. After technical approval of the proposal, a decision based on the direction of the research is then made and one Institute supports the project. Thus, other Institutes are interested in how the body protects itself against disease (the immune response) but our Institute is interested in the effects of aging on this system. Research projects that have this direction would be supported by our Institute. Research that focuses on a different aspect of the problem would be supported by the Institute having an interest in the particular area being studied.

APPLICATION OF RESEARCH FINDINGS

Mr. CONTE. As you noted in the opening statement, there are a great many Americans living in nursing homes and other facilities which are certainly less than desirable surrounding. What can this Institute do to help these people in their lifetime? Or is that asking too much, too soon?

Dr. GREULICH. Our Institute is wholly aware of the serious problems presently confronting our population of institutionalized older citizens. In several areas, such as the biofeedback and learning-memory areas, it seems possible that expansion of our research efforts

could result in relatively immediate and favorable impact. On the other hand, the vast majority of research questions now being pursued regarding the nature of the aging process are at present at a level of development far short of that which might be expected to have immediate application. Indeed, one might suggest that it is precisely for the purpose of speeding up the research process that the National Institute on Aging was created. Certainly, we take that challenge seriously.

Mr. CONTE. Would an increase in funding speed up the process or are you still too far back in basic research?

Dr. GREULICH. There is a clear need for both a continuation and expansion of basic research to all aspects of the aging process—biomedical, behavioral, social, economic, and so on. Only from a base of increased understanding of the fundamental issues can one expect to derive valid and effective means of alleviating the problems of our older citizens. Obviously, such an expanded effort will, in time, require more substantial resources, both dollars and people, than is currently at hand. With respect to the current year's request, there is no question that we can use every dollar effectively. The greatest immediate concern is the number of personnel available to carry out presently perceived opportunities in research promptly and effectively.

Mr. FLOOD. Thank you, gentlemen, we will adjourn.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Amounts Available for Obligation 1/

	1976 Estimate	1977 Estimate
Appropriation (Conferees Allowance).....	$17,526,000	$26,220,000
Request pending.....	1,762,000	---
Subtotal, adjusted appropriation.....	19,288,000	26,220,000
Comparative transfer from:		
"Office of the Director, NIH" (Transfer of funds for the Standard Level User Charge).	100,000	---
Total, obligations.....	19,388,000	26,220,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 comparable - $2,000; 1977 - $2,000.

National Institute on Aging

Budget Mechanism

	1976			1977		
	No.	FTE A/	Amount	No.	FTE A/	Amount
Grants						
Regular						
Non-competing	81		$7,997,000	64		$6,965,000
Competing	5		811,000	19		1,739,000
New	10		726,000	75		6,395,000
Supplemental	(1)		50,000	(4)		134,000
Subtotal	96		9,584,000	158		15,233,000
Special						
Research career programs	3		75,000	6		150,000
Scientific evaluation	---		24,000	---		42,000
Subtotal	3		99,000	6		192,000
Total, research grants	99		9,683,000	164		15,425,000
Fellowships						
Non-competing	16	22	375,000	10	16	286,000
Competing	---	---	---	---	---	---
New	7	14	261,000	26	33	645,000
Supplemental	---	---	---	---	---	---
Subtotal	23	36	636,000	36	49	931,000
Training grants						
Non-competing	10	69	1,126,000	6	41	659,000
Competing	---	---	---	---	---	---
New	---	---	---	---	---	---
Supplemental	---	---	---	---	---	---
Subtotal	10	69	1,126,000	6	41	659,000
Research and development contracts	18		1,202,000	23		1,642,000
Intramural research and direct operations	---		6,351,000	---		7,109,000
Standard Level User Charge	---		100,000	---		129,000
Program management	---		290,000	---		325,000
Total	150	105	19,388,000	229	90	26,220,000

A/ Full-time equivalents.

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN OF 1977 JUSTIFICATION

INSTITUTE: National Institute on Aging
(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. Aging	$7,997	$1,587		$99	$1,126	$636		$1,202		$12,647
2. Intramural research and direct operations							$6,351			6,351
3. Standard level user charge							100			100
4. Program management									$290	290
Total obligations	7,997	1,587		99	1,126	636	6,451	1,202	290	19,388

DHEW - National Institutes of Health

CROSSWALK - 1977 COLUMN OF 1977 JUSTIFICATION

INSTITUTE: National Institute on Aging
(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. Aging	$6,965	$8,268		$192	$659	$931		$1,642		$18,657
2. Intramural research and direct operations							$7,109			7,109
3. Standard level user charge							129			129
4. Program management									$325	325
Total obligations	6,965	8,268		192	659	931	7,238	1,642	325	26,220

Summary of Changes

1976 Estimated obligations	$19,388,000
1977 Estimated obligations	26,220,000
Net change	+6,832,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1976 pay increases and health benefits increases	---	$128,000	---	$+37,000
2. Within-grade pay increases	---	67,000	---	+70,000
3. Wage Board pay increases	---	60,000	---	+3,000
4. Bureau of Employee Compensation	---	5,000	---	+1,000
5. Increased cost of postage	---	20,000	---	+6,000
6. NIH service and supply fund increase	---	48,000	---	+17,000
7. Federal Telecommunications System charges	---	14,000	---	+3,000
8. Travel increase due to per diem change	---	85,000	---	+7,000
9. Gerontology Research Center maintenance contract	---	700,000	---	+18,000
10. Standard level user charge	---	100,000	---	+29,000
Subtotal	---	---	---	+191,000
B. Program:				
1. Research grants				
a. Noncompeting continuations	---	8,046,000	---	+2,088,000
b. Competing	---	1,637,000	---	+8,368,000
2. Fellowships				
a. Noncompeting continuations	---	375,000	---	+248,000
b. Competing	---	261,000	---	+645,000
3. Research contracts:				
a. Renewal	---	630,000	---	+572,000
b. New	---	572,000	---	+552,000
4. Intramural research and direct operations	168	6,451,000	---	+610,000
5. Program management	25	290,000	---	+31,000
Subtotal	193	---	---	+13,114,000
Total, program increases	---	---	---	+13,305,000

Summary of Changes - Continued

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
Decreases:				
A. Built-in:				
1. One day less pay	---	$3,798,000	---	$-10,000
Subtotal	---	---	---	-10,000
B. Program:				
1. Research grants				
a. Noncompeting completed, converted to competing or terminated	---	8,046,000	---	-3,077,000
b. Competing completed or converted to noncompeting	---	1,637,000	---	-1,637,000
2. Fellowships				
a. Noncompeting completed		375,000	---	-337,000
b. New converted to noncompeting	---	261,000	---	-261,000
3. Training grants				
a. Noncompeting completed	---	1,126,000	---	-467,000
4. Research contracts				
a. Renewal completed	---	630,000	---	-112,000
b. New converted to renewal	---	572,000	---	-572,000
Subtotal	---	---	---	-6,463,000
Total, decreases	---	---	---	-6,473,000
Total, net change	---	---	---	+6,832,000

Obligations by Activity

Page Ref.		1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
86	Aging.....	$10,252,000	$12,647,000	$18,657,000	$+6,010,000
	Positions	---	---	---	---
89	Intramural research and direct operations	5,539,000	6,351,000	7,109,000	+758,000
	Positions	168	168	168	---
	Standard level user charge.....	100,000	100,000	129,000	+29,000
	Positions	---	---	---	---
91	Program management....	280,000	290,000	325,000	+35,000
	Positions	5	25	5	-20
	Total obligations.....	16,171,000	19,388,000	26,220,000	+6,832,000
	Total Positions	173	193	173	-20

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	193	173	-20
Full-time equivalent of all other positions	35	43	+8
Average number of all employees	228	216	+12
Personnel compensation:			
Permanent positions	$3,137,000	$3,248,000	$+111,000
Positions other than permanent	165,000	256,000	+91,000
Other personnel compensation	70,000	75,000	+5,000
Subtotal, personnel compensation	3,372,000	3,579,000	+207,000
Personnel benefits	441,000	474,000	+33,000
Travel and transportion of persons	85,000	92,000	+7,000
Transportation of things	25,000	30,000	+5,000
Rent, communications, and utilities	45,000	67,000	+22,000
Printing and reproduction	40,000	60,000	+20,000
Other services:			
Project contracts	1,202,000	1,642,000	+440,000
Payment to NIH Management Fund	826,000	855,000	+29,000
Other	1,097,000	1,331,000	+234,000
Supplies and materials	500,000	675,000	+175,000
Equipment	310,000	400,000	+90,000
Grants, subsidies and contributions	11,445,000	17,015,000	+5,570,000
Total, obligations by object	19,388,000	26,220,000	+6,832,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1976 House Report	
1. The Committee directs that all resources necessary be made available to make this new Institute viable and effective.	1. During FY 1976, the NIA has brought together the resources and administrative, financial, grants, and program management staff to make the Institute a functional and viable organizational entity.
1976 Senate Report	
1. The Committee is seriously concerned that there is still no Director of the NIA.	1. The position of Director, NIA, is close to being filled. A firm offer has been made to and accepted by one of the candidates for this position. Final arrangements and clearances are in process.

Authorizing Legislation

Legislation	1977 Authorization	1977 Appropriation Requested
Aging:		
Public Health Service Act Title IV, Part H — National Institute on Aging.....	Indefinite	$24,630,000
Title IV, Part I — National Research Service Awards..	Indefinite	1,590,000

National Institute on Aging

COMPARABLE A/

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1975 B/	$14,728,000	$14,922,000 C/	$16,622,000	$15,822,000
1976	16,290,000	15,626,000 D/	20,626,000 D/	
Items not considered		(1,762,000)	(1,762,000)	
1977	26,220,000			

NOTES: A/ The figures presented in this table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding the Standard Level User Charge has been transferred to this institute in 1977. The amount for this item has been added to prior years for comparability purposes.

B/ Comparable amounts for aging (previously included within NICHD) for 1974 and previous fiscal years are not available due to the change in the budget activity structure from a mechanistic presentation to a programmatic presentation.

C/ Excludes amounts for research and development contracts which were not considered by the House due to the lack of authorizing legislation.

D/ Excludes amounts for training which were not considered due to the lack of authorizing legislation.

National Institute on Aging

ACTUAL

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1976	$16,190,000	$15,526,000 A/	$20,526,000 A/	
Items not considered		(1,762,000)	(1,762,000)	
1977	26,220,000			

NOTES: A/ Excludes amounts for training which were not considered due to lack of authorizing legislation.

Justification

National Institute on Aging

	1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Aging.....	$10,252,000	$12,647,000	$18,657,000	$+6,010,000
Positions	---	---	---	---
Intramural research and direct operations.....	5,539,000	6,351,000	7,109,000	+758,000
Positions	168	168	168	---
Standard level user charge	100,000	100,000	129,000	+29,000
Positions	---	---	---	---
Program management.....	280,000	290,000	325,000	+35,000
Positions	5	25	5	-20
Total obligations.....	16,171,000	19,388,000	26,220,000	+6,832,000
Total Positions	173	193	173	-20

General Statement

On May 31, 1974, the Research on Aging Act of 1974 (P.L. 93-296) was signed into law. Among the provisions of this act are: (a) the establishment of the National Institute on Aging (NIA) as the eleventh research institute at the National Institutes of Health; (b) the establishment of the National Advisory Council on Aging; and the requirement for development of a plan for a research program on aging within the Department of Health, Education and Welfare. In carrying out these provisions, the act states that the functions of the Institute are to conduct scientific studies of the aging process through grants, contracts and intramural laboratories; to measure the impact of all Department of Health, Education, and Welfare programs on the biological, medical, and psychological aspects of aging; to assure the training of adequate numbers of personnel in the field of aging; and to carry out public information and education programs on aging.

Although officially in operation since its formal establishment on October 7, 1974, the National Institute on Aging has only recently begun to function as a viable and independent organizational entity. The fiscal year 1977 budget request of $26,220,000 represents a significant step forward in carrying out the mandate of the Research on Aging Act to undertake comprehensive, systematic and intensive studies of the biomedical and behavioral aspects of aging and the related training of necessary personnel. Increases over the fiscal year 1976 amount are requested for all of the Institute's programs. The largest portion of the increase, however, will fund additional grants and contracts in several scientific areas that will produce additional information on the aging process.

Within the next 50 years, the number of persons in the United States over 65 will increase to 40 million from a current level of over 20 million. Two-thirds of the Federal money for 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 various diseases affecting the elderly, such as senile dementia, fecal and urinary incontinence, and calcium deficiencies in post-menopausal women. The dimensions of these problems are great, but nonetheless susceptible to diminution through research. It is the aim of the NIA research program to enable older Americans to enjoy good health and to remain participating members of society. The degenerative aging processes will be studied so that the debilitating effects of these processes can eventually be slowed or ameliorated.

In carrying out this research, the Institute utilizes several mechanisms. Within the aging program, project grants are awarded for research projects that are highly rated by the NIH peer review process. A fellowship program encourages manpower to enter the field of aging as researchers. Also, a research contracts program allows the Institute to target research to certain specified areas. Within the intramural research and direct operations activity, the Gerontology Research Center in Baltimore, Maryland, conducts clinical, behavioral and biomedical research of interest to the government scientists at work in this facility. Part of this effort includes a visiting scientist program that enables outstanding researchers from many parts of the world to pursue their scientific interests. In the direct operations area, support services are provided to all of the Institute's programs such as facilities support, review and approval of grants, procurement of equipment and animals, data processing services and printing costs. The program management activity provides personnel for the overall control and direction of the Institute's programs including program planning, budget, personnel, and space management, and other essential administrative functions. All of these activities are essential to a program which studies the aging process in a comprehensive and systematic way. Further details about the plans for each of these activities are contained in the pages that follow.

Aging

	1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Research grants:				
Regular	$7,850,000	$9,584,000	$15,233,000	+$5,649,000
Number	95	96	158	+62
Special	50,000	99,000	192,000	+93,000
Number	2	3	6	+3
Total, research grants	7,900,000	9,683,000	15,425,000	+5,742,000
Total number	97	99	164	+65
Fellowships	636,000	636,000	931,000	+295,000
Number	23	23	36	+13
Training grants	1,126,000	1,126,000	659,000	-467,000
Number	10	10	6	-4
Research and development contracts	590,000	1,202,000	1,642,000	+440,000
Number	9	18	23	+5
Total, aging	10,252,000	12,647,000	18,657,000	+6,010,000
Total number	139	150	229	+79

Purpose: The aging activity supports a nationwide research effort at universities, medical schools, hospitals, and other institutions in order to understand and alleviate the biological, medical, behavioral, and social impact of the aging process.

Budget policy, 1977: The budget request for fiscal year 1977 will provide for the continuation of ongoing research programs, the expansion of programs where promising leads have developed, and the launching of new aging research programs.

The Institute will expand its program of study of the biological basis of aging. It seems likely that many of the major difficulties of senescence are causally linked to the processes that go on in the development of individuals from fertilized eggs to adults. In that development one cell gives rise eventually to about 60 trillion cells. The several hundred cell types that develop are drastically different from each other and from the fertilized egg from which they evolved. In the process of becoming different many of their genetic possibilities have been repressed. In the repressed abilities may lie the mechanisms of eventual decline and death. In following this line of research, the Institute will make a major effort to link the experimental study of aging to the science of developmental biology.

The Institute will greatly expand its support of research on changes in the nervous system with age. These changes undermine a variety of human functions—sensation (sight, hearing, etc.), the motor activity necessary for everyday living and athletic excellence, the ability to alternate the fully awake state with satisfactory sleep, and various types of intellectual activity (learning, memory, problem-solving, etc.). Enough is already known to

demonstrate that all these functions decrease with age. Methods are available for studies on humans and experimental animals. The rat has been shown to exhibit progressive neurological loss with age. Studies of the changes in the rodent nervous system have led to an explanation of some of these changes. Thus the rat serves as a suitable experimental subject for studies of neurological decline. Further studies in both humans and animals will be conducted in fiscal year 1977.

The program of research on the various components of the connective tissues of the body which form bones, joints, and supporting tissues in almost all organs will be increased. These connective tissues are the sites of degenerative changes that lay the foundation for many chronic diseases of the elderly. The Institute's program on connective tissue at present is concentrated on collagen, the major connective tissue protein. It will be expanded to include work on the other major connective tissues such as elastic fibers and the large molecular matrices that give structure and strength to bones, joints, and skin.

It has long been established that certain classes of therapeutic drugs elicit unexpected responses when administered to elderly patients. Such paradoxical reactions are frequently opposite to the response which would normally be anticipated. An increasing volume of research now suggests that paradoxical reactions in elderly patients are far more frequent than has heretofore been believed, and that a wide spectrum of pharmacological agents share this behavior.

In view of the rapidly growing numbers of elderly patients receiving medical care — and with it treatment involving administration of an ever-increasing variety of drugs — it is imperative that a far more systematic research effort be undertaken to determine the causes of changes in drug sensitivity and response as a function of increasing patient age. The Institute will begin this research effort in FY 1977.

The Institute will expand its program on alterations in immunological function with age. It is known that there is a substantial decrease in such function as man and experimental animals grow older. Not all the consequences of these changes are known, but it is apparent that they may contribute to the occurence and severity of infections and cancer in the elderly. Suitable experimental animals are available for such studies, and it is already known that the manipulation of at least one variable—the level of caloric intake—alters the rate of the rise and subsequent decline of immunological competence across the lifespan. Support in this area will be increased.

The Institute will expand the support of commercial colonies of experimental animals. Most investigators wishing to study aging in experimental animals have difficulty in purchasing them, do not have the special facilities and expertise necessary to raise them, and, if they did raise their own animals, would have to wait for several years until the animals became old. The animals from NIA-supported colonies can be purchased by investigators with extramural funds. They have been a very valuable resource. This resource needs to be substantially expanded. Without such expansion, the progress of research on aging will be impeded.

Social studies supported by the Institute have dealt with individual adjustments to problems of aging and the changing age structure of the population. The Institute will begin a program concerned with a broader investigation of the impact of social factors on health. This is an area which will require much planning and especially detailed coordination with other Federal agencies.

A shortage of trained manpower is of significant concern in the field of aging research. Both individual postdoctoral fellowships and institutional type fellowships will be employed to fill the need. The institutional fellowships are particularly valuable because structured programs to fit the requirements of special research areas can be created.

One of the programs under consideration for initiation in FY 1977 is a special research grant program designed to provide funds to newly trained investigators for research in the field of aging. Over the past few years the interest of young people in the field of aging has increased significantly. However, because the field of gerontology is not well established in some of our nation's medical institutions there has resulted a shortage of adequately trained manpower. The program under consideration would address both of these factors by providing funds to young scientists so that they can pursue independent investigations during the formative stages of their research careers.

Intramural Research and Direct Operations

	1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Intramural research.....	$4,853,000	$5,241,000	$5,734,000	$+493,000
Positions	158	158	158	---
Direct operations.....	686,000	1,110,000	1,375,000	+265,000
Positions	10	10	10	---
Standard level user charge	100,000	100,000	129,000	+29,000
Positions	---	---	---	---
Total, intramural research and direct operations..	5,639,000	6,451,000	7,238,000	+787,000
Total, positions	168	168	168	---

Purpose: This activity includes the intramural research program of the Institute as well as such administrative functions as review and approval of grants, facility support costs and related general expense items essential to all of the Institute's research programs. The intramural program conducts research which has as its objective the improvement of the physical and mental health of our senior citizens in a way that will allow them to remain active and productive members of their families and communities. The research is performed by government personnel in the Gerontology Research Center (GRC) located in Baltimore, Maryland.

Budget Policy, 1977: During fiscal year 1977, the intramural program will continue its research efforts in such diverse areas as the study of physiological and genetic transfer systems; analysis of data on glucose tolerance, serum cholesterol, triglycerides and other factors obtained from the longitudinal study of 600 men; experiments which will lead to a better understanding of the deterioration of the immune system with age; and behavioral studies designed to improve self-sufficiency. Studies will be continued on the change in the metabolic rate of pharmacological agents with age.

Research on aging often requires experimental animals that, because of their age, are difficult and expensive to obtain. The GRC has therefore developed a large colony of aging rats for use as models in their studies of the aging process. Because the reliability of data gained from experiments utilizing these animals depends in part on the conditions under which they are housed, the GRC will upgrade its animal facilities. A portion of the requested increase will be used to renovate animal quarters, modernize caging, and improve animal husbandry. Implementation of this plan will help to ensure the reliability of data obtained in future experiments utilizing these animals.

Behavioral science research is directed towards understanding the factors which determine the decline in mental competence and self-sufficiency. Recent accomplishments at GRC in this area include behavioral training procedures which have enabled some patients to control their blood pressure and heart rate. One project has shown that patients suffering fecal incontinence due to certain physical problems can be taught fecal control. Additional funds will allow the beginning of clinical trials to determine the reliability and effectiveness of these biofeedback techniques in the control of cardiovascular disorders and fecal incontinence.

With increasing age, the immune system declines in its efficiency to combat diseases. Specific attention will be paid to the possibility that the immune system may be enhanced or "revitalized" by pharmacological agents. Further studies will be conducted to determine whether the decline in immune response is due strictly to age or, alternatively, to viral infections in the earlier years of life.

Further understanding of the role of cholesterol and other fatty substances in the genesis of atherosclerosis is of the highest significance because it is one of our nation's major health problems. The extension of the lipid research program in the setting of the current longitudinal aging study could be expected to provide data of basic importance to gerontologic research as well as to clinical medicine.

It is also expected that the intramural research program will participate in or carry out initiatives identified in the aging research plan currently being developed by the Institute.

In the direct operations area, the Institute anticipates the review and approval of an increased number of grant and contract applications, and will provide the essential support services required to implement the aging research plan.

Program Management

	1976 Revised Pres. Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Program management.....	$280,000	$290,000	$325,000	$+35,000
Positions	5	25	5	-20

Purpose: This activity provides the resources necessary to carry out the overall management and scientific direction of the Institute. Among the functions performed are financial, personnel and space management; program planning; coordination of all the Institute's activities; the review of current and proposed programs; and the dissemination of research information.

Budget Policy, 1977: The Institute will continue to provide for the overall management and scientific direction which was begun in fiscal year 1976. Since the Institute is now a viable organizational unit, it is expected that efforts in 1977 will be aimed at implementing the aging research plan and providing for the efficient management of an expanded program. One of the initiatives of this area will be the establishment of a program analysis capability to provide data on the effectiveness and balance of the various projects conducted by the Institute. Another effort will seek to improve the grants management functions of the Institute in anticipation of the increased workload which will result from the budget level requested in 1977. In line with the Institute's mandate from Congress, an expanded effort will provide for more effective dissemination of research information. All of these projects will help the Institute establish a firm foundation for its expanded scientific activities.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Program Purpose and Accomplishments

Activity: Aging (Public Health Service Act, Title IV, Part E, H and I)

1976 Estimate		1977		
			Budget Estimate	
No.	Amount	Authorization	No.	Amount
150	$12,647,000	Indefinite a/	229	$18,657,000

Purpose: The programs included within the aging activity are designed to support comprehensive and systematic studies of the medical, biological, behavioral and social aspects of aging and to provide for the training of adequate numbers of personnel.

Explanation: The aging activity includes those projects conducted in non-Federal facilities through grant awards to individual investigators; through fellowship awards directly to promising young researchers and to institutions that have designed particular research training programs; and through research contracts which allow the Institute to fill specific gaps.

Accomplishments in 1976: Research progress can be reported in several areas. At the cellular level a major finding has been the discovery that certain enzymes become less effective with age apparently because of a change in the structure of the enzyme rather than the quantity of the enzyme produced. Recent studies with rats suggest this animal may serve as a satisfactory model for studies of chemical and structural changes in brain function that are involved in human forgetfulness and ability to reason. Although follow up studies to show that restricting caloric intake delays deterioration of the immune system, the restriction of protein has an undesirable effect on the immune system. Studies on brain function indicate that a decrease in intellectual function occurs most severely in the very elderly and certain individuals rather than in all individuals.

Objectives for 1977: The Institute will continue viable ongoing research programs, expand programs where new findings need to be followed up and begin new efforts in aging research. Programs that will be expanded include the evaluation of the rat as a possible animal model for studying progressive neurological loss with age; studies relating to changes in connective tissue with age; follow up research on the finding that the intake of calories alters the immune response across a life-span; and the size of available colonies of aged experimental animals. New programs will include a study of unexpected drug responses in the elderly, a program concerned with the impact of social factors on the health of the aged and the possible initiation of a program designed to provide funds to newly trained investigators for research in the aging field.

a/ Extension of the National Research Service Award Act, Title IV, Part I, of the Public Health Service Act is currently pending before Congress.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Program Purpose and Accomplishments

Activity: Intramural Research and Direct Operations (Public Health Service Act, Title IV, Part H)

1976 Estimate		1977	
			Budget Estimate
Pos.	Amount	Authorization	Pos. Amount
168	$6,451,000	Indefinite	168 $7,238,000

Purpose: This activity supports the intramural research program review and approval functions of the Institute as well as providing support for the National Advisory Council on Aging.

Explanation: The intramural research activities of the Institute are carried out in the Gerontology Research Center located in Baltimore, Maryland. Basic research is conducted in order to obtain a fundamental knowledge of the aging process and to seek ways to improve the physical and mental health of our senior citizens in a way that will allow them to remain active and productive members of their families and communities. In addition, this activity provides the funds for the review and approval of grants, facility support costs and related administrative and general expense items essential to the research program.

Accomplishments in 1976: Research advances made by NIA scientists are providing the basic knowledge about aging that can eventually be used to guarantee a healthy and productive later life for all people. The Baltimore Longitudinal Study of Aging has continued to provide the primary resource for studies in man. Efforts have continued not only to provide basic data on age changes in individuals but also to probe into underlying mechanisms of these changes. Analysis of these studies showed a difference in the mortality of subjects who did or did not exercise regularly. Members of the group without exercise died two and one-half years earlier than the active group. As a result of conditioning techniques, patients with high blood pressure have been trained to voluntarily control their own blood pressures. Studies on senility indicate that there may be a memory-neurochemical correlation. If these findings hold up, improving memory by biochemical therapy may be a possibility in a few years.

Objectives for 1977: Basic research on the biological basis of aging will continue. Because research on aging requires experimental animals, the funding for this activity will be used to renovate animal quarters, modernize caging, and improve animal husbandry. Clinical trials will be initiated to determine the reliability and effectiveness of biofeedback techniques in the control of cardiovascular disorders and fecal incontinence. Further studies will be conducted to determine if age alone is responsible for the elderly's susceptibility to infection and cancer.

NATIONAL INSTITUTES OF HEALTH

National Institute on Aging

Program Purpose and Accomplishments

Activity: Program Management (Public Health Service Act, Title IV, Part H)

1976 Estimate			1977	
			Budget Estimate	
No.	Amount	Authorization	No.	Amount
25	$290,000	Indefinite	5	$325,000

Purpose: This activity provides the support necessary to carry out the overall management and scientific direction of the Institute.

Explanation: The Director and his immediate staff provide control and direction of the Institute's programs including budget, personnel, and space management; program planning; coordination of all the Institute's activities; the review of current and proposed programs; and the dissemination of research information.

Accomplishments in 1976: During 1976, the Office of the Director devoted a great deal of its resources to the establishment of the National Institute on Aging as an administratively independent, free-standing Institute within the National Institutes of Health. A program planning office has been established and continues to coordinate the development of a plan for a research program on aging within the Department of Health, Education, and Welfare.

Objectives for 1977: Resources will be used for continued establishment of the Institute and implementation of the research plan on aging. Activities planned for 1977 include the establishment of a program analysis capability within the Institute to provide data on program balance and effectiveness, the expansion of grants and contracts management activities to help insure the effective use of increased resources, and initiation of improved methods of disseminating research information.

National Institute on Aging

Transition Quarter Analysis

	Budget Authority by Activity			
	1976 Estimate		Transition Quarter	
	Pos.	Amount	Pos.	Amount
Aging	---	$12,647,000	---	$2,378,000
Intramural research and direct operations	168	6,351,000	168	1,563,000
Standard user level charge		100,000		25,000
Program management	25	290,000	5	82,000
Total, NIA	193	19,388,000	173	4,048,000

General Statement

The funds requested for the transition quarter are necessary to continue the National Institute on Aging programs at a rate approximating the level of effort supported by the fiscal year 1976 Continuing Resolution.

MONDAY, MARCH 1, 1976.

NATIONAL EYE INSTITUTE

WITNESSES

DR. CARL KUPFER, DIRECTOR
DR. DONALD S. FREDRICKSON, DIRECTOR, 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
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, 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 Eye Institute.

The presentation will be made by Dr. Kupfer, the Director.

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

[The biographical sketch of Dr. Kupfer follows:]

BIOGRAPHICAL SKETCH

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, National Institutes of Health. 1966–1970: professor and chairman in ophthalmology, University of Washington School of Medicine. 1962–1966: assistant professor in Ophthalmology, Harvard Medical School. 1960–1962: instructor in ophthalmology, Harvard Medical School. 1958–1960: research fellow in ophthalmology, Harvard Medical School. 1957–1958; research fellow in ophthalmology. Wilmer Eye Institute, the Johns Hopkins Medical School; laboratory assistant, biostatistics, the Johns Hopkins Medical School. 1953–1954: laboratory assistant, biostatistics, the Johns Hopkins Medical School. 1952–1954: 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; Pan American Ophthalmological Society.

Publications: Author or coauthor of over 50 publications in clinical ophthalmology and the anatomy, physiology and biochemistry of the visual system.

Mr. FLOOD. You have some people with you.

Dr. KUPFER. Yes, Mr. Chairman. On my left is Dr. William Raub, who is the Associate Director for extramural and collaborative programs; and on my immediate left is Mr. McManus, the executive

officer. Sitting behind Dr. Raub is Mr. Kenneth Cooke, our budget officer.

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

Dr. KUPFER. Yes, sir. Mr. Chairman and members of the committee: The National Eye Institute's program of research on major problems relating to blinding and disabling eye disorders is directed toward improving the quality of health care in this field. All research either conducted or supported by the Institute, from laboratory studies to clinical trials of new diagnostic and therapeutic techniques, is relevant to the achievement of this goal.

Statistics we have recently had compiled show that the cost to the Nation of blindness and other visual problems exceeds $5.2 billion a year. This includes direct costs, such as professional, medical, and hospital care, and estimates of lost earnings due to limited activity as a result of visual disability.

During the past year a number of important accomplishments were made through NEI support which are significant contributions to the improved prevention, diagnosis, and treatment of major eye problems. We hope that these and future developments will have a major influence on reducing the enormous economic as well as social costs of visual disorders.

CATARACT

In previous testimony I reported on exciting studies which have demonstrated not only the possibility of inducing cataracts in laboratory animals but the effectiveness of new drugs which can substantially slow down the formation of these opacities. Approximately 3 million Americans have cataract; more than 45,000 are blind from this disease. Each year, at least 300,000 cataract operations are performed at a cost of $750 million in medical, hospital, and followup care.

Now, National Eye Institute scientists have been able to induce in a new laboratory animal model a type of cataract very similar to that which occurs in some people with diabetes. Studies with this animal are helping show why cataract develops faster and at an earlier age in people with diabetes than in those without the disease. Powerful drugs have been formulated—and others are now being synthesized—which in preliminary testing have proved effective in retarding the formation of this type of cataract. These laboratory studies make us optimistic about the future possibility of slowing down the development of diabetic cataract by medical means, and we look forward to the eventual clinical trials of these new drugs.

Other studies during the past year have increased our understanding of the formation of the most common type of cataract, that associated with aging.

As I reported last year, research conducted by NEI-supported scientists at Columbia University and the Massachusetts Institute of Technology is helping explain how the transparency of the lens is normally maintained and how a breakdown in this process leads to cataract formation. Their studies have shown that the size and shape of lens proteins are important factors in determining lens transparency. In particular, they have found that clumping of lens protein causes scattering of light which leads to loss of lens transparency.

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These investigators now report that high concentrations of calcium may cause formation of the protein clumps. If this theory proves to be accurate, it may be possible to identify means of controlling the calcium and inhibiting the clumping process, thereby slowing down cataract formation so that surgery may not be required. We estimate that if the onset of cataract were delayed by an average of 10 years, the number of cataract operations performed annually could be reduced by 45 percent. This would amount to a yearly savings of approximately $337 million.

CORNEAL DISEASE

Other recent developments have a direct bearing on the improved treatment of corneal diseases. A new drug called ara-AMP has been shown by NEI-supported investigators at Harvard Medical School to be highly effective in treating deep-seated viral infections of the eyes of laboratory animals. This virus, herpes simplex, causes scarring of the cornea, and affects the eyes of nearly 300,000 Americans each year, causing blindness in many. In the 1960's the first drug used to treat any human viral disease—idoxuridine or IDU—was developed with NIH support. Ara-AMP promises to be much more effective than IDU or other current treatments for herpes infection, and trials are now underway to test the drug in humans. Since herpes simplex also is a major cause of severe venereal infection of the female genital tract, with resultant devastating effects on newborn children, ara-AMP is also expected to have an important bearing on this major public health problem.

A major advance in corneal transplantation was also made this year at the University of Florida by the development of a new tissue culture solution in which donor corneas can be preserved. The easily prepared solution permits fresh corneal tissue to be kept for periods of up to a week without need for freezing or other special handling. Prior to this development fresh tissue could be kept refrigerated for no more than 48 hours without deleterious effect. The new preservation technique promises to reduce the rate of corneal graft rejection by assuring healthier donor tissue. It is now being used by eye banks across the country, in some cases not only for storage of corneal tissue but for preparing fresh tissue for immediate use as a means of increasing the likelihood of a successful graft.

DIABETIC RETINOPATHY

In addition to research on diabetic cataract, the National Eye Institute has made a strong commitment to the support of clinical trials of treatments for diabetic retinopathy. A frequent complication of diabetes, this disease is characterized by abnormal growth of blood vessels on the retina. These may grow into the center of the eye and bleed. As a result, vision may be severely impaired. In particularly severe cases, permanent detachment of the retina may occur.

A clinical trial will soon begin of a new surgical technique called vitrectomy in which blood-clouded vitreous fluid is removed from the center of the eye. This extremely delicate operation has been successful in restoring vision to some people blind from diabetic retinopathy.

Vitrectomy has been made possible through the development of new surgical instruments, several of which had NEI support. At present, most ophthalmic surgeons wait a year after a hemorrhage has occurred before performing vitrectomy in order to give the eye a chance to clear on its own. The diabetic retinopathy vitrectomy study will test whether by performing this operation earlier, a better degree of vision than is now usually achieved can be restored.

In its initial phase, the vitrectomy clinical trial will involve seven clinics in various parts of the country; additional clinics are expected to be added within the year. Such studies, involving several research centers and considerable NEI staff resources, quite frankly, are expensive and difficult to carry out. Yet they provide valuable information essential to assuring the highest quality in medical care. In fact, controlled clinical trials are the best means of evaluating treatment for diseases which follow a variable course and for which the value of treatment cannot be objectively assessed through uncontrolled observation of small numbers of patients.

GLAUCOMA

In glaucoma research, a blood test that gives evidence of a systemic basis for this disease has been developed by investigators at Washington University in St. Louis. It has been known for some time that prolonged administration of corticosteroid eye drops, such as those commonly used to suppress ocular inflammation, can cause a rise in pressure within the eyes of certain individuals similar to that which occurs in open-angle glaucoma. Since the new test can show the same effect of corticosteroids in the test tube, it offers distinct advantages for the laboratory study of mechanisms which may underlie this disease. Such information would be extremely useful in the development of new antiglaucoma drugs which may be more effective than current treatments. It may even lead to means of preventing this disease which now affects nearly 800,000 Americans, more than half of whom are over age 65.

EFFECT OF EARLY VISUAL DEPRIVATION

Investigations by other scientists at Harvard Medical School, supported by National Eye Institute grants, have provided conclusive evidence that visual deprivation early in life can adversely affect the proper development and functioning of the visual nervous system. These findings may lead to a more complete understanding of such diseases as amblyopia known as lazy eye, and strabismus, known as wall-eye or cross-eye. The investigators have shown that while the structure and function of that part of the brain which processes visual information is genetically determined, environmental factors are important in determining how the brain responds to visual stimulation. Animal studies are now underway to determine whether visual deprivation early in life, such as may be caused by a congenital cataract in a human infant, may result in irreversible loss of visual brain cells. Such a discovery will help determine the correct early treatment of certain visual defects in the infant.

NEW INSTRUMENT FOR EYE RESEARCH AND DIAGNOSIS

The leading cause of blindness and visual disability in the United States is disease of the retina and its underlying vascular tissue, the choroid. To aid research in this important but difficult clinical area, the NEI has fostered development of a new instrument under contract with Johns Hopkins University. This device permits the simultaneous photography of blood flowing through the interrelated circulatory systems of the retina and choroid.

We expect that this new technique will provide valuable information about the interaction of the two circulatory systems in diseases such as diabetic retinopathy, macular degeneration, and sickle cell retinopathy, and how changes in blood flow might lead to the visual loss associated with these disorders.

PROGRAM PLANNING

In a report issued last year, "Vision Research Program Planning," the National Advisory Eye Council identified major research needs and opportunities in vision research that represented the findings of leading experts in each of the Institute's five major program areas. The planning process is continuing, building now upon the ground broken by the initial effort, and exploring in detail areas of research considered especially rich in opportunity for clinical payoff. In particular, the Council's planning subcommittee is seeking to identify, out of several possibilities, new programs which would have the broadest impact in improving the quality of eye care. These may include clinical trials of new methods of treatment and diagnosis. Workshops and symposia will be organized in selected areas of scientific research with particular emphasis on gaining input from areas of bioscience other than vision research that may be applicable to problems of the eye. Conversely, such gatherings will provide excellent forums for dissemination of important advances in vision research which are largely unknown outside this field but which could be of value to scientists working in other health research areas. The eye is a unique organ for discovery of information that cannot be easily gained elsewhere, but which may be of great importance to the solution of major disease problems occurring in other parts of the body.

An interim program planning document will be published this spring which will include updated data on national vision research support, and new information on the extent and costs of visual disorders. In the spring of 1977, a second major Council planning report will be published that will strongly influence the direction of our programs for the following 2 years.

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 1977 is $46,950,000. I shall be pleased to answer any questions and supply additional information the committee may desire for the record.

IMPACT OF REDUCED FISCAL YEAR 1977 BUDGET

Mr. Flood. Doctor, the 1977 budget for your Institute is $3,335,000 below the 1976 level. What is the impact of the reduction like that? What specific areas will be reduced?

Dr. KUPFER. Sir, there will be some reduction in all five program areas. As you know, we are concerned with retinal diseases, glaucoma, cataracts, corneal disease, and sensory-motor disorders, and there will be small reductions in all of these five areas.

The only program that is being protected is the clinical trial on the treatment of diabetic retinopathy using vitrectomy because a commitment has been made for this to get underway and additional funds will be necessary.

Mr. FLOOD. This budget also proposes to reduce the number of positions that were assigned to intramural research.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. What happens there? Does that reflect a shift in your research efforts from intramural to extramural research? I notice the number of your research contracts went up from 25 in 1976 to 30 in 1977. What is the situation?

STAFFING

Dr. KUPFER. The position shift really represents the fact that the positions that are in the appropriation bill for 1976 have not yet been distributed, and when they are distributed I think there will be an adjustment so that the decrease will not show. We are in the process of writing job descriptions, and as soon as the positions are made available we will be able to recruit.

Mr. FLOOD. Is there actually a shift from intramural to extramural?

Dr. KUPFER. No, sir. That just reflects this.

Mr. FORBUSH. I feel I must say that there will be no change in the 1977 budget. The fact is that the 1977 budget is based on the President's budget request for 1976, and it doesn't recognize that Congress did add to staff in 1976. But the 1977 budget will not be changed.

MAJOR RESEARCH NEEDS

Mr. FLOOD. You also mentioned that the National Advisory Council identified some major research needs in the vision field. Suppose you review briefly the areas identified by the Council.

Dr. KUPFER. Perhaps we might first look at each of the five program areas and pick out the particular area that the Council report identified as offering a unique research opportunity.

First of all, in the area of retinal disease, which is a major cause of blindness and visual disability, perhaps the largest, the Council has identified the need for more information concerning a single layer of cells that is just beneath the retina, which of course is the seeing part of the eye. This single layer of cells is called the pigment epithelium. In the last 5 years it has become apparent that this single layer of cells plays a very important role in the nourishment and the maintenance of a healthy retina.

There is suggested evidence that many of the degenerative conditions which occur in the retina may be related to the fact that this single layer of cells does not function as it normally should function. Yet we know very little about this single layer of cells, and therefore the Council has identified the need for more information, and this is now being implemented.

In the case of corneal diseases, there are really two areas that the Council has identified as requiring more activity. One is to study the cause of graft rejection. In the last 10 to 15 years the success of corneal

transplantation has improved from perhaps 30 percent to 80 percent, mainly through the use of new surgical techniques, and a better understanding of how the cornea functions. But there still remains a group of patients which cannot successfully be operated upon because the graft would be rejected, and therefore the Council identified this as a major need. We are now increasing investigations of the immunology of graft rejection.

Of course, this is a problem that exists in other portions of medicine, but in some respects it can be more easily and more directly studied in the case of the eye.

The second area of concern in the corneal area is the amount of visual disability that is due to the viral infection, herpes simplex. Corneal disease per se does not account for a large amount of blindness in this country but it is the most painful of all eye disorders. We have all had a foreign body in our eye, and we know how uncomfortable that is, and corneal disease gives the unremitting discomfort of irritation for hours, days, weeks, and even months.

The main cause of this in the United States is the virus herpes simplex, so that development of new drugs is being accelerated considerably.

In the area of glaucoma, we are particularly excited by two developments which the Council has identified. The first is that we now have an animal model in which the pressure in the eye can be elevated for prolonged periods of time, and this now means that we can study how increased pressure in the eye destroys the seeing nerve.

In the cataract program, studies would be conducted on the biological processes for maintaining normal lens hydration to determine how aberration in these mechanisms lead to cataract. Finally, studies of strabismus or crosseye, amblyopia, or misalignment of one eye due to disuse, as well as disorders of the oculomotor muscles, will be augmented in the sensory-motor program. In every major area of vision science, opportunities for the use of the controlled clinical trial are emerging. For example, this methodology is appropriate for evaluating the treatment of herpes simplex keratitis, the medical management of glaucoma, surgical techniques for removing cataract, management of proliferative diabetic retinopathy with photocoagulation, and the role of vitrectomy in preventing hemorrhage in patients with proliferative diabetic retinopathy.

CATARACTS

Mr. FLOOD. You mentioned that in your justification that the intramural research program has been able to delay the formation of the sugar cataracts in animals.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. When do you expect to be able to undertake the clinical trials?

Dr. KUPFER. There are two aspects of that program. There is a drug, and there is much enthusiasm to begin a clinical trial, but it is the determination of the scientists at the National Eye Institute that a much more powerful drug would be worth developing before important trials in patients are started. These drugs are now very actively being developed. So this is a very important and exciting possibility.

GLAUCOMA ANIMAL MODEL

Mr. FLOOD. Take a look at page 118 of your justifications. There you say, "Progress toward preventing glaucoma has been delayed for the lack of an appropriate animal model for this disease."

What about that?

Dr. KUPFER. Sir, to study a disease process it very often is extremely valuable to induce that disease in an experimental laboratory animal, which allows us to study what drugs or techniques are most effective in alleviating the disease.

As I was commenting before, we have finally been able to make two contributions in this area. The first is to be able to produce a model in an experimental animal in which pressure is elevated in the eye just as in the human in glaucoma.

Mr. FLOOD. When are you going to find the appropriate kind of animal model?

Dr. KUPFER. We have it now, sir. That is what I am saying.

Mr. FLOOD. Certainly that will be a job for your Institute to insure a supply of that animal.

Dr. KUPFER. This technique has been picked up by many investigators throughout the country, as well as other countries throughout the world, and there is increased research now being done to determine how the increased pressure in the eye does damage the optic nerve. So I think we are going to have some answers coming through in the next 2 to 3 years concerning this effect.

EFFECT OF BRIGHT LIGHTS ON THE EYE

Mr. FLOOD. Here is one we have noticed very recently in the news media. What do we know about injury to the eye due to exposure to bright lights, excessive exposure to sunlight, both?

Dr. KUPFER. Mr. Chairman, there is no doubt that very high levels of illumination can potentially be detrimental. I think if we take the one extreme of the individual who gazes at the sun, we know that in that situation an actual burn can be created in the retina, and this individual will lose vision.

Mr. FLOOD. I think that is pretty generally accepted now by the public finally.

Dr. KUPFER. Yes, sir. It is also true that in a variety of experimental animals kept in levels of illumination that are quite bright, retinal degeneration does occur, but I must say that to date there is no evidence that any high level of illumination is detrimental to the human retina.

MICROWAVE AND ULTRAVIOLET INJURIES TO THE EYE

Mr. FLOOD. Are you working with the National Institute of Occupational Safety and Health to determine if microwaves causes injuries to the eye?

Dr. KUPFER. Yes, sir. As you know, we do have liaison with this organization, especially in the area of microwaves——

Mr. FLOOD. I am speaking now of the National Institute of Safety and Health.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. You are working with them.

Dr. KUPFER. They recently held a meeting dealing with ultraviolet light and microwaves, and we have had representatives from the National Eye Institute at that meeting. This involvement goes back many years.

Mr. FLOOD. I would like you for the record to develop—you don't have to do it right now—the answer with reference to ultraviolet light. There is a developing interest in that, a startling awareness all of a sudden.

[The information follows:]

ULTRAVIOLET EXPOSURE

Ultraviolet exposure of the eye may result in painful corneal burns and blindness. During World War II eye damage was substantial among unprotected shipyard workers who were exposed to welding arcs. Daylight levels of ultraviolet light, however, are absorbed by the cornea of the eye and the fluid which flows behind it. Very little penetrates as far as the lens or vitreous, and none reaches the retina. Anyone engaged in activities in which exposure of the eyes to high levels of ultraviolet radiation would be well-advised to use protective goggles.

OCCUPATIONAL HAZARDS

Mr. FLOOD. By the way, what are some of the most significant occupational hazards to the eye?

Dr. KUPFER. I think the most significant occupational hazard is still the potential of eye injury in light and heavy industry on the one hand, and in automobile accidents on the other. Automobile accidents account for a significant amount of blindness through trauma in the young age group, and even though there have been major developments on safety glass in automobiles, injuries about the head very often result in damage to one or both eyes.

Mr. FLOOD. That is far more than an occupational hazard, but I am speaking particularly of occupational hazard.

Dr. KUPFER. That would most likely occur when the rules governing safety goggles are not observed.

DISSEMINATION OF INFORMATION

Mr. FLOOD. Last year told us that you planned to intensify your own activities to inform the general public and the practicing physicians. We have been asking all the institutes this.

What specifically are you doing in that area? Not just the public but the physicians as well.

Dr. KUPFER. Perhaps I might go down the list of some of the things we have done in this past year. First of all, following our great interest in diabetes and the causes of blindness and disability this disease can cause, an exhibit was placed at the meeting of the American Academy of Ophthalmology and Otolaryngology in Dallas last September. The results to date of the clinical trial on the treatment of diabetic retinopathy was presented and discussed with ophthalmologists. About two thirds of all the ophthalmologists in the United States attended that meeting, and I would say the vast majority of those present attended this exhibit.

In addition, a motion picture film was prepared by the National Eye Institute on the clinical trial for the treatment of diabetic retinopathy, and this has been distributed to a number of departments of ophthalmology throughout the country for showing to practicing physicians.

We are going to have an exhibit at the American Diabetes Association this June in San Francisco to inform the diabetologists about the eye complications of diabetes and what we are doing to treat this condition. This is another example of the interdisciplinary aspect of dissemination of research information.

Last June the National Eye Institute held a science writers seminar attended by over 30 science writers. We discussed the programs of the National Eye Institute in the various areas of research, and highlighted again the activity in diabetic retinopathy. There were nearly 50 newspapers and other publications that reported this activity.

Finally, of course, the vision research program planning report, which I think you are familiar with has been widely disseminated. As a matter of fact, there have been mailings to 12,000 ophthalmologists and schools of optometry.

Mr. FLOOD. I have seen that in two or three very surprising places.

Dr. KUPFER. It has been widely disseminated, not only among the practicing ophthalmologists and other related eye-care professionals but to the scientific community and, when requested, to the general public.

We have been very active in trying to convey the research activities that we are doing and how they are translated into improved diagnosis and treatment.

GLAUCOMA

Mr. FLOOD. In your justifications you also cite—and let me quote—"Glaucoma is responsible for 14 percent of all new cases of blindness." What are the main research possibilities of reducing that rate?

Dr. KUPFER. Sir, one of the major developments in the last year has been the ability to identify the individual who may be at a particularly high risk of not only developing glaucoma but having damage to his or her optic nerve. This is done by a blood test. This is of great significance because it is much easier to obtain a small specimen of blood and do some very elaborate tests to determine whether this individual is at high risk than to do a battery of clinical tests, none of which are very objective.

Mr. FLOOD. You take the blood from where?

Dr. KUPFER. Normally the arm, but in fact, it can also be developed from a finger stick.

I think this is a major development. We want to identify those people who are at high risk, because the reason why patients with glaucoma become blind is not a problem of diagnosis and control, which we can do, but that the disease has gone undetected.

Mr. FLOOD. You seldom hear the plural use of glaucoma. We just say glaucoma. Are some kinds of glaucoma more susceptible to early detection than other kinds?

Dr. KUPFER. Yes, sir. That is a very appropriate question. There are many glaucomas.

Mr. FLOOD. That was a leading question.

Dr. KUPFER. Yes, sir. The type of glaucoma that is very often associated with in our mind is the glaucoma that occurs in an individual that is accompanied by severe pain, rainbows around lights, and loss of vision. Interestingly enough, this type of glaucoma can be cured if caught within the first 18 hours after the pain begins.

Mr. FLOOD. What kinds, then, of glaucoma offer the most attractive opportunity for research?

Dr. KUPFER. The one that affects the most people is the one that is referred to as open angle glaucoma. This is the one where everything appears to be normal, yet the pressure is too high in the eye. Congenital glaucoma can be cured if treated early; the narrow angle type can be cured; but open angle is the most difficult to detect because it is painless.

Mr. FLOOD. There is such a thing as cataract by trauma; is there glaucoma trauma?

Dr. KUPFER. One can find increased intraocular pressure following blunt trauma to the eye, and again this usually can be detected early because such an individual very often seeks help from an ophthalmologist.

Mr. FLOOD. I was thinking of boxers, to begin with.

Dr. KUPFER. There are two complications for the boxers. One is glaucoma and the other is retinal detachment.

THE OCUSERT

Mr. FLOOD. You mentioned last year ocusert—I thought it was a French term, but apparently it is not—to improve the delivery of the pressure-lowering drugs. Let me quote this: "Ocusert, to improve the delivery of pressure-lowering drugs to the eyes of glaucoma patients."

Is that being generally accepted as a mode of therapy? If it is, is it within the economic reach of the patients you intend to use it for?

Dr. KUPFER. There is no doubt now that the ocusert is a very effective way of providing the eye with medication for a prolonged period of time, 2 weeks let us say.

Mr. FLOOD. What is the derivation of the term ocusert? I didn't ask you that last year. I should have.

Dr. KUPFER. I think ocu refers to ocular and sert is probably insert. It is inserting the drug.

Mr. FLOOD. I figured it out myself. I wanted you to say so.

Dr. KUPFER. So I think the concept has been proven.

What we want to see now is the use of other more potent drugs in treating glaucoma.

Mr. FLOOD. What about the economic reach?

Dr. KUPFER. It is much more expensive to use the Ocusert to place drops in the eye but I think, like so many other things, as more and more Ocuserts are used, the price will probably come down.

Mr. FLOOD. Within reach?

Dr. KUPFER. Yes.

Mr. FLOOD. Take a look at the justifications.

"Glaucoma results when there is an obstruction in the outflow of a fluid aqueous humor."

GLAUCOMA

In the areas of basic research again, what is being done to further get an understanding of the production of a fluid and any process having to do with obstruction?

Dr. KUPFER. National Eye Institute investigators, and several others outside the Institute, remove small pieces of this outflow area when we do surgery on patients with glaucoma to try and determine what has happened to make this tissue abnormal.

I would like to add one other thing. There is the hope that examining this tissue will provide a link between the blood tests that I have mentioned before and the extreme sensitivity to steroids and the abnormality that exists in the outflow channels in glaucoma.

AQUEOUS HUMOR PRODUCTION

Mr. FLOOD. Well, I am concerned about the production of the fluid.

Dr. KUPFER. The fluid production is normal.

Mr. FLOOD. What about the obstruction?

Dr. KUPFER. We know there is an obstruction, but we do not know how it comes about. We hope to determine this by growing this tissue in culture.

Mr. FLOOD. That is certainly basic research.

Dr. KUPFER. Very much so.

ANTIGLAUCOMA DRUGS

Mr. FLOOD. Has there been any recent progress in the development of any new antiglaucoma drugs?

Dr. KUPFER. I would say that there is at present the hope of developing some new drugs that will decrease the amount of fluid being produced in the eye that has glaucoma. The amount of fluid that is produced is normal, but it cannot leave the eye.

Mr. FLOOD. Can you imagine the headline, "Drug To Stop Glaucoma!"

Dr. KUPFER. I think we are away from that at the moment. But I think we can have a heading, "Drug To Control Glaucoma."

Mr. FLOOD. I will settle for that right now.

Dr. KUPFER. Yes, sir; I think we do have a number of very effective drugs.

Mr. FLOOD. For the time being.

Dr. KUPFER. For the time being and new ones are being developed.

PHOTOGRAPHIC TECHNIQUES

Mr. FLOOD. All right. Now, last year you said, "We are developing techniques to photograph the back of the eye, the optic nerve."

That was what you used for clinical diagnosis technique.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. To assist in the very early detection of glaucoma?

Dr. KUPFER. Yes, sir.

Mr. FLOOD. All right. What progress are you making in this area?

Dr. KUPFER. A camera has been developed that will be able to photo-

graph the optic nerve, the seeing nerve of the eye, to determine whether any damage has been done. This camera will first be tested on normal volunteers, and then on patients, to see whether these defects can be detected. This testing phase is beginning.

ARTIFICIAL LENS IMPLANTS

Mr. FLOOD. Are artificial lens implants now the accepted practice?

Dr. KUPFER. Yes, sir.

Mr. FLOOD. We have heard about those for years for cataract patients. That has come to our attention very, very recently as quite a thing, although we have heard talk about it for quite a long time.

What is the position of your Institute with reference to these devices, or drugs, whichever is the appropriate thing to call them?

Dr. KUPFER. Yes, sir. Well, the National Eye Institute can only say that until the intraocular lens is tested in a scientific manner by clinical trial methodology, it is not possible for us to say whether they are of greater benefit than the conventional cataract surgery, which, as you know, is successful 90 to 95 percent of the time.

VITRECTOMY

Mr. FLOOD. You mentioned this last year again, but you also brought up in your statement this year surgical treatment of the eye by this new procedure of vitrectomy.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. We understand that is being evaluated. It's in an initial phase, I suppose.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. Rather extensively controlled trial, I would hope. Better elaborate on that.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. I take it it is a very extensive clinical trial.

Dr. KUPFER. Yes, sir. You are quite right. There is no doubt that vitrectomy is of great use in restoring eyesight to patients with diabetic retinopathy in whom a hemorrhage has occurred inside the eye.

But until now it was necessary for such a patient to wait about 1 year after the hemorrhage had taken place before the operation was done. This is quite a long period of time for an individual.

Mr. FLOOD. Because of the clot?

Dr. KUPFER. Yes, sir. There is mounting evidence that perhaps not only can the operation be done sooner than 1 year, but there may even be a benefit to doing it earlier in preventing a second hemorrhage. We are beginning a clinical trial to compare early vitrectomy within the first 3 or 4 months after memorrhage, and late vitrectomy after 1 year to see which is the better approach to such a patient.

LASER USE IN OPHTHALMOLOGY

Mr. FLOOD. We hear a lot of discussion about lasers in everything. Has the National Eye Institute evaluated this tool with reference to eye diseases?

Dr. KUPFER. The laser has several applications in ophthalmology. I think one is that it can treat certain types of glaucoma and avoid surgery.

We can use the laser as a cutting instrument, if you will, to perform surgery without entering the eye.

A second more extensive use is that of the laser for the treatment of diabetic retinopathy. The new vessels that grow can be sealed using the laser beam. The use of the laser is also being evaluated in a rather large clinical trial which is at present being very carefully evaluated.

Mr. FLOOD. I first became acquainted with laser beams, on Defense appropriations on which I serve as well, and now I hear you people talking about this thing. It is quite a circle.

Dr. KUPFER. Yes, sir.

DIABETES RELATED RESEARCH

Mr. FLOOD. Now, as you know, the Diabetic Act emphasized that, among other things, diabetes is a significant cause of blindness.

Dr. KUPFER. Yes, sir.

Mr. FLOOD. That is pretty well accepted by the public too. Well, you did touch on it, but maybe you can tell us briefly something about your progress in the diabetic retinopathy unit.

Dr. KUPFER. Yes, sir. To even further strengthen that statement, diabetic retinopathy is probably the leading cause of new adult blindness in the United States today.

If it isn't the first, then it is very close to being the first, so it is a major problem.

Mr. FLOOD. What does that phrase mean, "new adult"?

Dr. KUPFER. Blindness occurring in the adult as opposed to children.

Mr. FLOOD. You mean all of a sudden?

Dr. KUPFER. I mean adults who have been reported blind for the first time within a given year.

Mr. FLOOD. OK.

Dr. KUPFER. We have made a very large commitment to our program in diabetic retinopathy. We are spending approximately $5.2 million.

Mr. FLOOD. You are making it clear blindness in an adult is not necessarily a progressive condition.

Dr. KUPFER. Well, sir, in the case of diabetic retinopathy, the disease is progressive. However, in some patients, depending on the stage of their condition, vision may be permanently lost within a matter of days. In other patients, visual loss may follow a more variable and slower course.

HERPES SIMPLEX

Mr. FLOOD. Now, you mention a new drug called ARA–AMP.

Dr. KUPFER. Yes. sir.

Mr. FLOOD. You say: "To be highly effective in treating deep-seated viral infections, herpes simplex of the eyes of laboratory animals."

Dr. KUPFER. Yes, sir.

Mr. FLOOD. Well, that certainly sounds very promising. Do you have any kind of preliminary results this afternoon?

Dr. KUPFER. No, sir. I think there is a clinical trial that will shortly begin between two or three centers in the United States to evaluate this drug in human cases.

The herpes virus either affects the surface of the cornea, in which case it is relatively easy to control, or it invades the deeper part of the cornea, in which case it is very difficult to control. It is the second group of patients that we hope will benefit by this new drug.

Mr. FLOOD. Mr. Roybal?

EFFECTS OF EARLY VISUAL DEPRIVATION

Mr. ROYBAL. Thank you, Mr. Chairman.

Doctor, you indicated that visual deprivation early in life can adversely affect the proper development and functioning of the visual nervous system.

Dr. KUPFER. Yes, sir.

Mr. ROYBAL. What does that really mean?

Dr. KUPFER. If a child is born with a congenital cataract, which prevents light from reaching the retina, it becomes very critical to know when that cataract should be removed. There is now evidence to suggest that if light does not fall upon the retina within a critical period of time, when the child is an infant, then changes will take place in the nervous system that will prevent that child from using the eye effectively later in life.

Mr. ROYBAL. Does that mean then that child has a potential for difficulty as an adult?

Dr. KUPFER. For that eye, yes, sir. Now, of course, many of these children have cataracts in both eyes, so it becomes even more critical when the cataract is removed.

CATARACTS

Mr. ROYBAL. Now, in the drugs that you have developed or have been developed for the control of cataract, have any been developed that are useful in that particular instance?

Dr. KUPFER. For congenital cataract?

Mr. ROYBAL. Yes, sir.

Dr. KUPFER. No, sir, the only cataract we can now control with drugs is the cataract that occurs in diabetics.

Mr. ROYBAL. I misunderstood what you had been saying, and I am glad this was clarified.

Now, what about the aftereffects of these drugs, for those who do have diabetes? Are there any aftereffects?

Dr. KUPFER. Well, sir, we have not tried these drugs in patients who have diabetic cataracts, so it is still in the animal testing stage, but we are very confident that these drugs are very safe, fortunately. Therefore, there is every reason to believe that a very large safety margin exists.

Mr. ROYBAL. If they are so safe, why haven't they been tried on people?

Dr. KUPFER. We want to make the drug more potent because the ideal way to give the drug would be in the form of drops, because it would then just be acting at the site, where one would want the drug to act.

Mr. ROYBAL. But the research then is going on at the moment?

Dr. KUPFER. Very actively, sir.

Mr. ROYBAL. How much is it costing?

Dr. KUPFER. Well, the entire program for cataract research is about $4 million, and I would say this part might be perhaps 25 percent, or $1 million. It is a very small program, and it should be perhaps much larger considering the magnitude of the problem.

ADEQUACY OF BUDGET

Mr. ROYBAL. It seems to me that it should be much larger. I am glad that you brought up the fact that you also agree that it should be much larger.

This brings me then to my last question, and I am concerned about the fact that you are requesting $46.95 million. Last year you received $45.56 million. Now that, in my opinion, does not take care of inflation. What happens then? Are you curtailing some of your work?

Dr. KUPFER. Well, I think we are doing what we and the National Advisory Eye Council have identified as the highest priority areas.

Mr. ROYBAL. But, I asked you if you were curtailing some of your work?

Dr. KUPFER. Well, perhaps I would phrase it in terms of that we are doing what has to be done, but perhaps not moving as rapidly as we might wish to move, but I think we are doing what we feel must be done.

You know, there is the extent of research you do and there is the rate with which you can do it. I would say we probably are covering what we should be, but perhaps not moving ahead fast enough.

Mr. ROYBAL. What you are telling the committee is you are doing the best you can under the circumstances.

Dr. KUPFER. Yes, sir.

Mr. ROYBAL. And circumstances are not very good. More money could be put into this work, so that you could proceed more rapidly. And essentially do more for humanity, but the truth of the matter is that you don't have the availability of funds necessary to do the work as you would like to see it done. Is that a correct statement?

Dr. KUPFER. Yes, sir.

Mr. ROYBAL. Thank you, Doctor.

Mr. EARLY. Just one question, Doctor, following Mr. Roybal's last question. As far as proceeding efficiently, at an increased rate, what level of appropriation would you need to be able to spend money at the same efficiency with the same productivity as you have this past year? An estimate would be good enough.

Dr. KUPFER. Well, perhaps it might be appropriate to refer again to this document, in which the National Advisory Eye Council made a recommendation that they felt would be an appropriate level of funding to carry on research that had been identified as high priority. One would then come up with an estimate of approximately $75 million.

Mr. EARLY. $75 million?

Dr. KUPFER. Yes, sir. This is the budget developed by the National Advisory Eye Council.

Mr. EARLY. What other particular research programs do they include in their recommendation of $75 million that you are not presently implementing?

Dr. KUPFER. I had mentioned earlier in my opening statement that we in the United States spend approximately $750 million a year on cataract extractions and we are spending $4 million on all cataract research.

Well, about one-half of 1 percent, and it seems to me that one would be in a much better position reaching a goal of slowing down the rate of cataract development if there were a major expansion in the cataract area, and I think the National Advisory Eye Council has recommended that.

I think the same thing is true of retinal disease, which accounts for one-third of all of the blindness in the United States, that there are perhaps broader opportunities. There is also the opportunity to move more rapidly in the research that I had mentioned to the Chairman on pigment epithelium. This is the critical layer of cells which seems to be so very vital to the health of the retina, the seeing part of the eye.

I think in the case of evaluation of new forms of treatment, the clinical trial methodology should be expanded to test new drugs, to test the intraocula lenses the chairman raised, to test other new developments so we know the quality of care the American public receives is the very, very best.

RAMIFICATIONS OF FUNDING LEVEL

Mr. EARLY. Can you tell me, Doctor, with regard to cataract and retina research and these forms of treatments, is the brain power available in the research areas now?

Dr. KUPFER. Yes, sir.

Mr. EARLY. So, would any of those particular researchers be in an area of unemployment right now?

Dr. KUPFER. Well, perhaps I could quote you some figures based upon 1977 budget estimate. We would be funding about 25 percent of the research grants that were approved by review. And, of course, this would suggest that there are a number of individals who will not be funded by the National Eye Institute.

We know that we support 80 percent of all of the vision research done in the United States.

Mr. EARLY. Doctor, would you be able to supply for the record the number of people that will be relieved of their jobs with this 6.6-percent reduction in research in fiscal 1977?

Dr. KUPFER. Yes, sir, I will be happy to.

Mr. EARLY. Would you care to estimate what that would be?

Dr. KUPFER. We would make an estimate of this. Of course, this is very difficult, but we could make an estimate.

UNEMPLOYMENT DUE TO DECREASED BUDGET

We estimate that approximately 243 people will be relieved of their jobs with a decreased budget in fiscal year 1977. Of course, these people might become teachers, administrators in universities, or they might simply enter private industry. There is actually no way that we can determine which ones will continue without employment, but we do know that with NIH supporting 86 percent of all vision research

in this country, the probability of many of these individuals continuing research in the field of visual disorders is very minute.

Mr. EARLY. How much money is being spent on research in this current fiscal year?

Dr. KUPFER. Well, sir, the 1976 appropriation figure is $50,285,000.

Mr. EARLY. So we are reducing that by $3.3 million?

Dr. KUPFER. That would be reduced to $46,950,000, which is what I am requesting for fiscal 1977.

Mr. EARLY. A reduction of $4 million, but did you not say that only 25 percent of your research projects would be continued?

Dr. KUPFER. Yes, sir; I am sorry. Perhaps I might clarify that. The original discussion dealt with research grants.

Mr. EARLY. Would you identify the amount of money?

Dr. KUPFER. Yes, sir. In 1976 we will spend $34,486,000 in research grants. I am requesting from the Congress for fiscal year 1977 $30,926,000.

Mr. EARLY. Why a reduction?

Dr. KUPFER. I think that this is a figure which reflects what we can use to continue to do what has to be done in as efficient a manner as possible.

RESEARCH GRANTS PROGRAM

Mr. EARLY. Is that going to call for the cessation of any of your present grants?

Dr. KUPFER. Well, as I said, if we look at those two figures, the $34,486,000 and the $30,926,000, our estimate at the present time, we will only be able to fund 25 percent of the grants that would have been approved for 1977.

Dr. FREDRICKSON. New and competing.

Dr. KUPFER. Yes, sir.

Dr. FREDRICKSON. You must understand, Mr. Early, that the grants that are now in force, and for which our commitment is not due to expire this year, will all continue. That base will be maintained. A certain number of grants, for which the commitment period has expired, will come up for their competing renewal. And there will be, in addition, new grants for projects that will receive support for the first time.

Mr. EARLY. Can you provide a dollar figure for grants in effect right now, for fiscal 1977, without getting into the expanded ones? Just what is in effect now, what will that cost be?

Dr. KUPFER. Sir, perhaps I might read it this way. In the present fiscal year we are spending $26,999,000 on grants that are in the process of running for several years, that were approved last year, or the year before, or before that, and are running in continuity.

Next year we will honor those commitments and spend $26,582,000, approximately the same amount.

Now, what about those grants that are running for a 2- or 3- or 4- or 5-year period, and then come up for renewal, and we call those competing renewal grants. Now, this year we will be able to fund $4,429,000 of those grants.

These are investigators who have been actively supported for anywhere between 3 and 17 years of their research career.

Next year we will only be able to fund $3 million worth of those grants.

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And finally there is the individual who is entering research for the first time, and, of course, this represents the new blood, the new ideas.

Or perhaps, Dr. Fredrickson reminds me, there are even old investigators with new ideas that may be submitting a grant for the first time. This year we are funding $3.008 million.

Mr. EARLY. So that appears to be, according to your text, very heartily underfunded.

Dr. KUPFER. Yes, sir. That drops to $1.294 million in fiscal 1977. So what I am saying is that we will, of course, continue to fund those investigators to whom a commitment had been made for them to conduct their research for a period of time.

Mr. EARLY. Won't there be grants, Doctor, that you are now developing, that may put you in another direction and may need more and more research? And, won't you be unable to continue in those directions at these budget levels?

Dr. KUPFER. Yes, sir.

Mr. EARLY. That is all, Mr. Chairman.

DIABETES RELATED RESEARCH

Mr. CONTE. Have you been working with any other Institutes on the link between diabetes and eye disease?

Dr. KUPFER. Yes. The National Diabetes Mellitus Research and Educational Act of 1974 established the Diabetes Mellitus Coordinating Committee to coordinate Institute research activity in diabetes and to establish channels for the communication and exchange of information necessary to support a coordinated comprehensive diabetes program.

Within the National Institutes of Health several Institutes, including the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Heart and Lung Institute, National Institute of Child Health and Human Development, National Institute on Aging, National Institute of General Medical Sciences, National Institute of Dental Research, and the National Eye Institute, sponsor diabetes related research and belong to this committee. Information concerning progress made by one Institute in diabetes research is disseminated to other investigators working in the diabetes research area.

The Diabetes Act also called for the establishment of a Diabetes Commission to develop a long-range plan for diabetes. The membership of this Committee also reflects an inter-Institute cooperative effort in that 7 of the 17 members of this group were National Institutes of Health Institute Directors. As a member of this Commission, I actively participated in the development of the long-range plan for diabetes research. As the basis for the eye research portion of this interdisciplinary plan, in June of 1975, members of the National Eye Institute's staff jointly conducted a workshop on occular complications of diabetes with the Commission on Diabetes in order to highlight research advances to date and to delineate future areas of concentration.

Finally, in the intramural research program of the National Eye Institute, selected research protocols are conducted, utilizing expertise provided across Institute lines.

DISSEMINATION OF INFORMATION

Mr. CONTE. Do you have any formal mechanism for dissemination of information regarding eye care? How do you plan to make this information available?

Dr. KUPFER. The National Eye Institute's program of dissemination of research information on eye care is conducted by a branch of the Institute responsible for all scientific reporting and public information activities. The National Eye Institute Office of Program Planning and Scientific Reporting prepares and distributes information on eye care to the general public, scientists engaged in vision research, practicing ophthalmologists and optometrists, students, members of voluntary and professional organizations, and other interested individuals and groups.

Many approaches are utilized in disseminating such information. One principal means is direct communication. The Institute responds to thousands of written and telephone inquiries each year from the public concerning eye care. The National Eye Institute also publishes fact sheets and brochures about eye care which are made available on request. The availability of these publications is advertised through press releases, radio and television spot announcements, and the General Services Administration's Consumer Information Center.

Other means for disseminating information on eye care are exhibits at scientific and medical meetings, and direct mailing of reports to members of vision research and medical organizations. The National Eye Institute also participates in the information dissemination programs carried out centrally at the National Institutes of Health, including the annual National Institutes of Health Open House, "Search for Health" newspaper columns, News and Feature Service, utilized by more than 500 publications and writers, and the annual publication "Research Advances." The Institute also holds press conferences in order that timely newsworthy information can be disseminated quickly to the general public through the mass media. In addition, the National Eye Institute always responds promptly to the frequent press inquiries it receives concerning its own programs as well as the general field of eye care and research.

The National Eye Institute engages from time to time in other special dissemination activities, a recent example of which is the National Eye Institute contribution to the Health, Education, and Welfare Bi-Cent-Ex exhibit in Washington which features recent advancements in the treatment of eye disease.

RETINAL DISEASES FUNDING LEVEL

Mr. CONTE. My figures show that 32 percent of blindness occurs due to reinal and choroidal diseases. What percent of the Eye Institute's budget concerns these diseases?

Dr. KUPFER. In fiscal year 1977, the National Eye Institute will spend approximately 33 percent of its funds on diseases of the retina and choroid.

CATARACTS

Mr. CONTE. Has any further work been done on cataracts problem as it relates to aging? Does this research overlap National Institute of Aging?

Dr. KUPFER. The Institute is directing a considerable amount of its research resources toward determining what causes cataract and finding a means of slowing down the progression of the disease.

National Eye Institute supported investigators at Columbia University and the Massachusetts Institute of Technology have found that the size and shape of proteins in the lens are important factors in determining the transparency of this tissue. By measuring the amount of laser light scattered by different lenses outside the eye, these scientists found that aggregates or clumps of protein in the cataractous lens are over 50 times larger than those in the normal lens.

The same investigators are now looking at what causes this protein clumping. They have found that one type of lens protein, alpha-crystallin, is implicated in the development of lens opacities associated with aging. Their research shows that in one kind of cataract, there is a reduced content of low molecular weight proteins along with an increase in insoluable protein in the lens.

Recent studies also indicate that calcium may play a role in protein clumping. Investigations have shown that there is marked increase in concentration of calcium at the time of the development of lens opacities. There is further evidence that calcium may help cause this transformation of proteins from normal low molecular weight to clumps of high molecular weight. Investigators hope to identify a means of controlling the calcium and thereby inhibiting the clumping process. If this can be achieved, it may become possible to slow down the formation of cataract and greatly reduce the need for surgery.

There is no overlap between the cataract research supported by the National Eye Institute and the work being done by the National Institute of Aging. Certainly, however, much of the cataract problem relates to the aging process. Because cataract is a problem unique to the eye, cataract research is assigned to the National Eye Institute. The Institute does maintain liaison with the new Aging Institute where appropriate.

VITRECTOMY

Mr. CONTE. The justification states that you have been exploring a new technique called vitrectomy. Can you tell us the significance of this operation?

Dr. KUPFER. In order to explain the significance of this operation, I think I should first define the vitreous and the conditions that lead to visual loss in patients who would benefit from vitrectomy. The significance of the operation will then become clear.

The vitreous is the clear, jelly-like fluid which fills the center of the eye. The health and transparency of the vitreous can be affected directly by disease, aging, or injury. The vitreous may also be affected by diseases of the retina, the light-sensitive tissue at the back of the eye. Diabetic retinopathy, for example, can cause the retina to bleed into the vitreous or can cause the formation of a lattice work of fibrous materials at the back of the vitreous. Both conditions interfere with the transmission of light and can even damage the retina. The result in both cases is visual loss.

Until recently, surgical removal of the diseased vitreous —vitrectomy—had been considered too risky to attempt in most cases. However, during the past 5 years, a number of researchers—many working with the support of the National Eye Institute—have begun to refine vitrectomy and to design new instruments for performing the opera-

tion. For example, instruments which simultaneously cut the vitreous, remove it from the eye, and replace it with a clear solution, so the eye will not lose its shape, have been developed. In time, the solution is naturally replaced with a clear, watery fluid which normally circulates in the front part of the eye.

It seems clear from clinical observations that vitrectomy can often increase the visual function, sometimes dramatically, of eyes which have been blind for a year or more as a result of severe vitreous hemorrhage. The prognosis for spontaneous clearing of such vitreous hemorrhages is poor and the clearing resulting from vitrectomy can be immediate. Based on these observations, it has been suggested that vitrectomy should be used sooner in eyes with extensive vitreous hemorrhage, without requiring the patient to wait for the elapse of some arbitrary time.

The National Eye Institute is therefore conducting a controlled clinical trial to evaluate early vitrectomy in diabetic retinopathy. The National Eye Institute is also supporting and conducting studies to learn more about the vitreous in health and disease and to gain additional information about the use of vitrectomy for treating certain diseases of the eye.

Vitrectomy is being performed with increasing frequency. Many patients with severe visual impairment have had enough vision restored by the operation to move about with ease; a few have regained sufficient vision to read. However, the operation provides no guarantee against recurring hemorrhages and visual impairment. In addition, vitrectomy is not suitable for all patients with vitreal disease or retinal diseases that affect the vitreous. Any patient interested in vitrectomy should consult his or her own ophthalmologist for specific advice.

JUTIFICATION OF BUDGET LEVEL

Mr. CONTE. If up to $1 billion of lost income is caused by blindness every year; if 1 out of every 20 Americans suffer uncorrectable visual impairment and one-half million Americans are legally blind, how do you justify a cut of over $3.3 million?

Dr. KUPFER. In terms of research, those areas which have been identified by the National Advisory Eye Council as deserving increased emphasis will be protected, especially our program in diabetic retinopathy, which is the second leading cause of blindness in the United States. In addition, the Institute will be able to maintain the momentum generated by all its programs in fiscal year 1976.

REHABILITATION AIDS

Mr. CONTE. Does your Institute conduct and support research into the possibilities of help to those already blind?

Dr. KUPFER. Yes, we do. Many forms of blindness, most notably cataract and some corneal conditions are quite amenable to correction through surgery. National Eye Institute supported investigations have led to dramatic improvements in the treatment of both conditions. Just this year, for example, we have reported the development by a grantee at the University of Florida of a new tissue culture solution which holds great promise for improving the outcome of corneal transplantation procedures.

Many individuals blind as a result of bleeding within the eye caused by diabetes are now being helped by a new operation called vitrectomy, made possible by new surgical instruments. The National Eye Institute has played a major role in the development of these devices and is about to launch a major multi-center clinical trial to determine when in the course of diabetic eye disease, diabetic retinopathy, vitrectomy may be of most benefit in restoring vision to blind people.

Although the major support of research to assist blind people who cannot benefit from medical treatment is carried out by the Health, Education and Welfare's Office of the Blind and Visually Handicapped, the National Eye Institute does fund a few projects to enhance the mobility of visually handicapped persons. One of these is the development of a device which can translate visual images into patterns of mechanical stimulation on the skin, a process analogous to "finger writing" which children often like to do. The feasibility of this approach has already been demonstrated. Current development is aimed at refining the technology of the device and evaluating its adaptability to serving the daily needs of the blind individual.

CLINICAL TRIAL IN VITRECTOMY

Mr. CONTE. How much will the clinical trial study of the vitrectomy technique cost?

Dr. KUPFER. The National Eye Institute's clinical trial of vitrectomy will cost approximately $1 million a year. It is planned that all phases of the trial will be completed by 1980.

The major costs of the trial relate to standardized data collection at each of 10 participating clinical centers, and centralized coordination, recordkeeping, and data analysis at a participting Fundus Photography Reading Center and a coordinating center. Study funds are not utilized for physician fees or hospitalization costs.

Mr. CONTE. Is there a less expensive way to test it?

Dr. KUPFER. There is no less expensive way to evaluate vitrectomy as a vision-restoring technique in patients with diabetic retinopathy. There are a possible 300,000 people who might be eligible for vitrectomy surgery at a estimated cost of about $3,000–$4,000. Thus, at a cost of $1 million per year, we are evaluating an operation that may add as much as $1,200 million to U.S. health care costs.

The trial has the minimum requirements of (1) adequate number of patients, 750–1,000, (2) recording of many variables, clinical observations, and operative evaluations, (3) adequate facilities for handling large amounts of data and for the subsequent statistical analysis of these data, and (4) a separate center for the bias-free evaluation of photographs of the eye, which are required for objective documentation of the physical effects of the treatment. Observations of patients must be made repeatedly over a prolonged period, thus substantially increasing the volume of data to be processed and analyzed. This includes monitoring both for adverse and beneficial effects of treatment which is essential for protection of patients, an accepted ethical principle for clinical trials.

Thus, multiple clinical centers and associated organizations for data handling and analysis are required to achieve the objectives above.

Mr. FLOOD. Well, thank you very much.

Dr. KUPFER. Thank you, Mr. Chairman.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Amounts Available for Obligation

	1976	1977
Appropriation	$45,565,000	$46,950,000
Request pending	4,647,000	---
Subtotal, adjusted appropriation	50,212,000	46,950,000
Comparative transfer from:		
"Office of the Director, NIH: (Transfer of standard level user charge)	+73,000	---
Total obligations	$50,285,000	$46,950,000

National Eye Institute

Budget Mechanism

	1976			1977		
	Number	FTE[1/]	Amount	Number	FTE[1/]	Amount
Grants						
Regular						
Noncompeting	432		$26,999,000	445		$26,582,000
Competing	85		4,429,000	58		3,000,000
New	58		3,008,000	25		1,294,000
Supplemental	(4)		50,000	(5)		50,000
Subtotal	575		34,486,000	528		30,926,000
Special						
Scientific evaluation	--		97,000	--		125,000
Academic Investigator Awards	11		300,000	11		300,000
Research career program	25		620,000	25		620,000
Subtotal	36		1,017,000	36		1,045,000
Total grants	611		35,503,000	564		31,971,000
Fellowships						
Individual:						
Noncompeting	79	79	1,178,000	70	70	1,053,000
Competing renewals	--	--	--	27	27	400,000
New	18	18	275,000	--	--	--
Supplemental	--	--	--	--	--	--
Institutional:						
Noncompeting	20	80	1,200,000	20	80	1,200,000
Competing renewals	--	--	--	--	--	--
New	--	--	--	--	--	--
Supplemental	--	--	--	--	--	--
Total fellowships	117	177	2,653,000	117	177	2,653,000
Training Grants						
Noncompeting	19	51	1,994,000	12	32	1,187,000
Supplemental	--	--	--	--	--	--
Total training grants	19	51	1,994,000	12	32	1,187,000
Intramural Research and Direct Operations	149		7,569,000	138		8,344,000
Research and Development Contracts	25		2,322,000		30	2,522,000
Program Management	3		171,000	3		180,000
Standard Level User Charge	--		73,000	--		93,000
Institute Total	152		$50,285,000	141		$46,950,000

DHEW - National Institutes of Health

Crosswalk - 1976 COLUMN OF 1977 JUSTIFICATION

National Eye Institute
(Dollars in thousands)

Program	Research Grants				Training Grants		Intramural Research and Direct Operations	Research and Development Contracts	Program Management	Total
	Non-competing	Competing	Special Multi-disciplinary Centers	Other	Grants	Fellowships				
Retinal & Choroidal Diseases	9,744	2,578	--	586	283	899	--	2,125	--	16,215
Corneal Diseases	4,768	1,144	--	100	693	185	--	--	--	6,890
Cataract	3,186	576	--	73	360	87	--	--	--	4,282
Glaucoma	4,397	952	--	85	539	391	--	197	--	6,561
Sensory-Motor & Rehabilitation	4,904	2,237	--	173	119	1,091	--	--	--	8,524
Intramural Research & Direct Operations							7,642		--	7,642
Program Management								--	171	171
Total	26,999	7,487	--	1,017	1,994	2,653	7,642	2,322	171	50,285

DHEW - National Institutes of Health

Crosswalk - 1977 COLUMN OF 1977 CONGRESSIONAL

National Eye Institute
(Dollars in thousands)

Program	Non-competing	Competing	Multi disciplinary Centers	Other	Training Programs Grants	Training Programs Fellowships	Intramural Research and Direct Operations	Research and Development Contracts	Program Management	Total
Retinal & Choroidal Diseases	9,943	1,257	--	614	404	942	--	2,403	--	15,565
Corneal Diseases	4,277	460	--	100	243	637	--	28	--	5,745
Cataract	2,443	1,042	--	73	132	150	--	--	--	3,840
Glaucoma	3,446	942	--	85	141	507	--	91	--	5,232
Sensory-Motor & Rehabilitation	6,453	643	--	173	265	147	--	--	--	7,951
Intramural Research & Direct Operations							8,437	--	--	8,437
Program Management								--	180	180
Total	26,582	4,344	--	1,045	1,187	2,653	8,437	2,522	180	46,950

Summary and Explanation of Changes

1976 Estimated Obligations	$50,285,000
1977 Estimated Obligations	46,950,000
Net Change	-$ 3,335,000

	1976 Pos.	1976 Amount	Change Pos.	Change Amount
Increases:				
A. Built-in				
1. Within-grade salary increase	--	$45,000	--	+ $45,000
2. FTS rate increase	--	33,000	--	+ 5,000
3. Bureau of employees compensation	--	4,000		+ 1,000
4. Increased cost of postage	--	33,000	--	+ 1,000
5. Payment to NIH Management Fund	--	2,981,000	--	+ 679,000
6. Annualization of October 1975 pay increase	--	3,231,000	--	+ 37,000
7. Increased per diem	--	84,000	--	+ 20,000
8. Standard Level User Charge	--	73,000	--	+ 20,000
Subtotal	--	--	--	+$808,000
B. Program				
1. Research grants				
a. Noncompeting continuations	--	26,999,000	--	+ 7,487,000
b. Competing (new continuations and supplementals)	--	7,487,000	--	+ 4,344,000
c. Special: Scientific Evaluation	--	97,000	--	+ 28,000
2. Fellowships				
a. Noncompeting continuations	--	2,378,000	--	+ 275,000
b. Competing (new continuations and supplementals)	--	275,000	--	+ 400,000
3. Research and Development Contracts	--	2,322,000	--	+ 200,000
Total increases	--	--	--	+13,542,000
Decreases:				
A. Built-in				
1. One less day of pay	--	3,213,000	--	-13,000
2. Decrease of eleven (11) positions	152	--	-11	--
Subtotal	152	3,213,000	-11	-13,000
B. Program				
1. Research grants				
a. Noncompeting completed or converted to competing status	--	26,999,000	--	- 7,895,000
b. Competing completed or converted to noncompeting	--	7,487,000	--	- 7,487,000
2. Fellowships				
a. Noncompeting completed or converted to competing status	--	2,378,000	--	- 400,000
b. Competing completed or converted to noncompeting	--	275,000	--	- 275,000
3. Training grants				
a. Noncompeting completed or converted to competing status	--	1,994,000	--	- 807,000
Total decreases	--	--	--	-16,877,000
Total, Net Change	--	--	--	-$3,335,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Pos.	1976 Revised President's Budget Amount	1976 Appropriation Pos.	1976 Appropriation Amount	1977 Estimate Pos.	1977 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Retinal and Choroidal Diseases....	--	$14,070,000	--	$16,215,000	--	$15,565,000	--	-$ 650,000
	Corneal Diseases.....	--	5,779,000	--	6,890,000	--	5,745,000	--	- 1,145,000
	Cataract.....	--	3,717,000	--	4,282,000	--	3,840,000	--	- 442,000
	Glaucoma.....	--	5,645,000	--	6,561,000	--	5,232,000	--	- 1,329,000
	Sensory-Motor Disorders & Rehabilitation.....	--	7,301,000	--	8,524,000	--	7,951,000	--	- 573,000
	Intramural Research & Direct Operations.....	138	7,752,000	149	7,569,000	138	8,344,000	-11	+ 775,000
	Program Management.....	3	171,000	3	171,000	3	180,000	--	+ 9,000
	Standard Level User Charge.....	--	73,000	--	73,000	--	93,000	--	+ 20,000
	Total Obligations	141	$44,508,000	152	$50,285,000	141	$46,950,000	-11	-$3,335,000

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	42	41	-1
Full-time equivalent of all other positions	1	1	-
Average number of all employees	40	39	-1
Personnel compensation:			
Permanent positions	$1,322,000	$1,305,000	-$17,000
Positions other than permanent	200,000	210,000	+10,000
Other personnel compensation	150,000	188,000	+38,000
Subtotal, personnel compensation	1,672,000	1,703,000	+31,000
Personnel benefits	41,000	45,000	+4,000
Travel and transportation of persons	120,000	140,000	+20,000
Transportation of things	5,000	4,000	-1,000
Rent, communications and utilities	157,000	170,000	+13,000
Printing and reproduction	10,000	13,000	+3,000
Other services:			
Project contracts	2,322,000	2,322,000	-200,000
Payment to NIH Management Fund	2,981,000	3,680,000	+699,000
Other	649,000	746,000	+97,000
Supplies and materials	357,000	388,000	+31,000
Equipment	300,000	305,000	+5,000
Grants, subsidies and contributions	40,150,000	35,811,000	-4,339,000
Total obligations by object	$50,285,000	$46,950,000	-$3,335,000

AUTHORIZING LEGISLATION

Legislation	1977 Authorized	1977 Appropriation Requested
Public Health Service Act Section 301 -- Research and Investigations in General	Indefinite	
Title IV, Part F -- National Eye Institute	Indefinite	$43,110,000 2/
Title IV, Part I -- National Research Service Award Act	1/	$ 3,840,000 2/

1/ Authorization expired June 30, 1975, extension legislation is pending.

2/ Funding estimate only.

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	42,608,000 4/	50,000,000 4/	
Items not considered		(4,647,000)	(4,647,000)	
1977	46,950,000			

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 as authorized by P.L. 93-192.

3/ Excludes Research and Development contracts not considered by House due to lack of authorizing legislation.

4/ Excludes National Research Service Awards not considered by the House or Senate due to lack of authorizing legislation.

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	42,608,000 4/	50,000,000 4/	
Items not considered		(4,647,000)	(4,647,000)	
1977	46,950,000			

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 as authorized by P.L. 93-192.

3/ Excludes Research and Development contracts not considered by House due to lack of authorizing legislation.

4/ Excludes National Research Service Awards not considered by the House or Senate due to lack of authorizing legislation.

* "The figures presented in this Table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of General Research Support Grants is no longer the function of this Institute. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes."

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Justification

National Eye Institute

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Retinal & Choroidal Diseases	--	$14,070,000	--	$16,215,000	--	$15,565,000	--	-$ 650,000
Corneal Diseases	--	5,779,000	--	6,890,000	--	5,745,000	--	- 1,145,000
Cataract	--	3,717,000	--	4,282,000	--	3,840,000	--	- 442,000
Glaucoma	--	5,645,000	--	6,561,000	--	5,232,000	--	- 1,329,000
Sensory-Motor Disorders & Rehabilitation	--	7,301,000	--	8,524,000	--	7,951,000	--	- 573,000
Intramural Research and Direct Operations	138	7,825,000	149	7,642,000	138	8,437,000	-11	+ 795,000
Program Management	3	171,000	3	171,000	3	180,000	--	+ 9,000
Total	141	$44,508,000	152	$50,285,000	141	$46,950,000	-11	-$3,335,000

General Statement

The mission of the National Eye Institute is to conduct, foster, and support research and research training on disorders of the eye and visual system. Therefore, gaining new knowledge about the normal functioning of the eye and visual system, as well as its pathology, and a clearer understanding of the sciences underlying vision, is essential to progress against the major causes of blindness and visual disability.

Working to this end, the National Eye Institute supports, through grants, fellowships, and contracts to medical schools and research institutions, research and research training aimed at improving the prevention, diagnosis, and treatment of vision disorders; conducts laboratory and clinical research in its own facilities and fosters statistical and epidemiological studies of visual disorders in human populations; fosters research on the rehabilitation of the visually handicapped; encourages the application of research findings to clinical practice; heightens public awareness of vision problems; and cooperates with voluntary organizations which engage in related activities.

The objective of this research is to increase knowledge needed to deal with visual problems which cost the Nation over five billion dollars annually. (This according to a recent study conducted by contract for the National Eye Institute.)

EFFECTS OF EYE DISEASES ON AMERICANS

Social

The are feared by Americans more than any other affliction, save cancer;

They have caused nearly one-half million Americans to be classified as legally blind;

They are the reason why 10 million American citizens--one of every 20--suffer from significant and uncorrectable visual impairment;

One and one-half million Americans are so severely visually impaired that they cannot read a newspaper with either eye, even with glasses.

Economic

Up to $1 billion of lost income annually due to blindness;

$500 million annual costs to public welfare agencies for services to blind people.

INCIDENCE AND PREVALENCE OF VISION DISORDERS

	Number of People Afflicted	Number of Blind Persons	Number of Newly Blind Each Year	Percent of all Blindness
Retinal and Choroidal Diseases	1,177,000	151,000	15,000	32%
Corneal Diseases	311,000	22,000	N/A [1]	6%
Cataract	3,013,000	64,000	4,400	14%
Glaucoma	1,016,000	56,000	3,100	12%
Sensory-Motor Disorders of Vision	890,000 [2]	36,000	3,000	9%
Other Causes	4,708,000	138,000	N/A [1]	27%

[1] Not available.

[2] Nerve atrophy and myopia only.

Research activities supported by the Institute are currently grouped under five major research activities: Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma, and Sensory-Motor Disorders and Rehabilitation.

Institute scientists and grantees are engaged in research to advance understanding of vision and to attack the full range of those vision disorders affecting large segments of the population.

Advances in vision research supported by the NEI have made significant inroads against visual disability and blindness in recent years. 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.

In a recently completed program planning effort, a detailed analysis of the National Eye Institute's programs was conducted by a committee of the National Advisory Eye Council. The council is a board of twelve citizens appointed by the Secretary of Health, Education and Welfare who represent the fundamental and medical sciences, education, and public affairs. The Council advises, consults with, and makes recommendations to the Secretary and the Director of the National Institutes of Health on matters relating to the activities of the National Eye Institute. In the conduct of this analysis the committee identified needs and opportunities where significant research advances in vision research can be expected in the near future. Therefore, the prime objective of the National Eye Institute in FY 1977 will be to continue to address those needs and opportunities identified by the above committee in an effort to provide a sound scientific basis for alleviating the deprivation associated with impaired eyesight and blindness. Specific objectives are delineated under the appropriate program activity.

Still, much more research needs to be conducted if we are to reduce the grim statistics already mentioned and reduce the costs associated with visual diseases and blindness for the American people.

Retinal and Choroidal Diseases

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research Grants:								
Regular: -								
Noncompeting	163	$ 9,744,000	163	$ 9,744,000	172	$ 9,943,000	+9	+$ 199,000
Competing	13	690,000	50	2,578,000	24	1,257,000	-26	- 1,321,000
Special	15	483,000	19	586,000	19	614,000	--	+ 28,000
Subtotal	191	10,917,000	232	12,908,000	215	11,814,000	-17	- 1,094,000
Fellowships	31	745,000	37	899,000	39	942,000	+2	+ 43,000
Training Grants	3	283,000	3	283,000	3	406,000	--	+ 123,000
Research & Development Contracts	24	2,125,000	24	2,125,000	28	2,403,000	+4	+ 278,000
Total		$14,070,000		$16,215,000		$15,565,000		-$ 650,000

Retinal and Choroidal Diseases

Introduction

Diabetic retinopathy, macular degeneration, retinitis pigmentosa, and other retinal degenerative diseases are primary causes of more than one third of all blindness in this country. These diseases which can neither be prevented nor cured, are considered by ophthalmologists to be the most difficult to treat and most in need of further research.

An estimated 15,000 people become blind each year from retinal and choroidal diseases, which already accounts for 32% of all blindness in the U.S.

Progress against these diseases has been severely impeded by the lack of knowledge of fundamental processes underlying retinal function. In response to this need, the National Eye Institute is conducting and supporting laboratory studies to unravel the complexities of retinal function in health and disease. Institute-fostered investigations include studies to understand better the mechanism of the retina's response to light and the initial processing of information that is transmitted to the visual centers of the brain, as well as developing animal models of various retinal diseases.

NEI studies are also aimed at elucidating the cause of retinal degenerations and evaluating the effect of laser therapy in retinal diseases. The Institute-supported Diabetic Retinopathy Study is designed to evaluate the effectiveness of photocoagulation, a treatment employing an intense beam of light such as that emitted from the laser, in preserving vision in patients with diabetic retinopathy. This study is the first one designed to access adequately the effectiveness of photocoagulation treatment in a large number of patients.

One new area being explored is vitrectomy, or the surgical removal of vitreous, the clear, jelly-like substance which fills the center of the eye. Research supported by the NEI has already yielded new instrumentation for this procedure, and consideration is now being given to show how this new approach can best be exploited primarily in diabetic retinopathy.

Financing

This program is funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Program Plans for 1977: Additional research will be supported on the pigment epithelium, a one-cell thick layer of tissue behind the retina, because of the basic relationship of this tissue to normal retinal function, and its potential importance in such visual disorders as retinitis pigmentosa, macular degeneration, and retinal detachment. Other studies will focus on how the retina is organized for the complex processing of visual information, the role of blood flow in the retina and underlying choroid in retinal degenerative and vascular disorders, the development of animal models for inflammatory diseases of the choroid and retina, correlations between clinical observation and laboratory analysis of diseased retinal and choroidal tissue and clinical research.

Under the requested level approximately 196 research grants, of which 24 are new and competing will be awarded to address the needs and opportunities presented above. Additionally, 39 fellowships, 3 training grants, and 28 research contracts will be awarded.

Corneal Diseases

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research Grants:								
Regular:								
Noncompeting	61	$4,768,000	61	$4,768,000	63	$4,277,000	+2	-$ 491,000
Competing	1	55,000	22	1,144,000	9	460,000	-13	- 684,000
Special	4	100,000	4	100,000	4	100,000	--	--
Subtotal	66	4,923,000	87	6,012,000	76	4,837,000	-11	- 1,175,000
Fellowships	6	163,000	12	185,000	29	637,000	+17	+ 452,000
Training Grants	5	693,000	5	693,000	2	243,000	-3	- 450,000
Research & Development Contracts	--	--	--	--	1	28,000	+1	+ 28,000
Total		$5,779,000		$6,890,000		$5,745,000		-$1,145,000

Corneal Diseases

Introduction

Corneal diseases are a leading cause of blindness worldwide and are the most painful of eye disorders. There are an estimated 22,000 Americans blind from corneal disease, 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.

One of the most difficult corneal diseases to treat is that caused by the herpes simplex virus. Often recurring, herpes simplex infections of the eye account for more sickness and loss of vision than any other corneal infection in Western countries. To combat this problem, the Institute is supporting research to improve drug treatment of herpes simplex infections of the cornea.

Other areas of research being emphasized by the Institute include studies of immunologic mechanisms, corneal opacification, edema, and better means of drug therapy. Additional important areas of corneal research include epidemiologic investigations, studies of the tear film, and tumor virology and immunology.

Financing

This program is funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Program Plans for 1977: Tissue culture and biochemical analysis of abnormal human corneal tissue removed at the time of corneal transplantation will be pursued in order to learn more about corneal diseases in humans. Major problems related to increasing the success rate of corneal grafts will be addressed.

Under the requested level approximately 72 research grants, of which 9 are new and competing will be awarded to address the needs and opportunities presented above. Additionally, 29 fellowships, 2 training grants, and 1 research contract will be awarded.

Cataract

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research Grants:								
Regular:								
Noncompeting	52	$3,186,000	52	$3,186,000	42	$2,443,000	-10	-$743,000
Competing	1	56,000	11	576,000	20	1,042,000	+9	+ 466,000
Special	3	73,000	3	73,000	3	73,000	--	--
Subtotal	56	3,315,000	66	3,835,000	65	3,558,000	-1	- 277,000
Fellowships	3	42,000	7	87,000	7	150,000	--	+ 63,000
Training Grants	4	360,000	4	360,000	1	132,000	-3	- 228,000
Research & Development Contracts	--	--	--	--	--	--	--	--
Total		$3,717,000		$4,282,000		$3,840,000		-$442,000

Cataract

Introduction

Any cloudiness, or opacity, in the normally transparent lens is called a cataract. The more serious types of cataract will obstruct the passage of light to the retina and impair vision. Although there are different types of cataract, the most common are those associated with old age, the so-called senile cataract.

Nearly 3,013,000 Americans have cataract, 64,000 of whom are legally blind. Therefore, ways are being sought to prevent cataract or medically retard its progression. Although surgery is 95% successful, social, psychological, and economic factors contribute to cataracts being responsible for 14% of all blindness in this country. With a cataract operation costing about $2,500, the 400,000 procedures performed annually cost about $1 billion. For these reasons, the Institute is fostering research aimed at prevention and non-surgical treatment of cataract. Recent advances in understanding the chemistry of cataract formation offers hope that this goal may be achieved.

Research conducted on the Bethesda campus into the type of cataract associated with diabetes (sugar cataract) has led to the prevention of this form of lens opacity in the test tube and the delay of its formation in living animals. Investigations are underway in congenital cataract as well, and research has shown that an inactivating substance present in the lens is responsible for congenital cataract formation in mice. Studies are also continuing into the formation of the cataract associated with aging. With age there occurs an increase in heavy molecular weight proteins formed by an aggregation process. The increase in the large proteins in cataract causes light scattering and may be the basis of opacification of the lens. Currently detailed studies on the process of aggregation is being undertaken. In addition, methods to prevent the aggregation of lens proteins are being explored. These studies open the possibility of both prevention and non-surgical treatment of this major cause of blindness.

Financing

This program is funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Program Plans for 1977: Investigations on the biological processes for maintaining normal lens hydration will be conducted to determine how aberrations in these mechanisms lead to cataract. Studies of protein changes in the lens in the development of senile cataracts will also be conducted. The search for new animal models for studying congenital cataracts will be intensified. Additionally, studies to find alternate methods for optical rehabilitation of cataract patients will be conducted.

Under the requested level approximately 62 research grants, of which 20 are new and competing will be awarded to address the needs and opportunities presented above. Additionally, 7 fellowships, and 1 training grant will be awarded.

Glaucoma

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Decrease or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research Grants:								
Regular:								
Noncompeting	45	$4,397,000	45	$4,397,000	50	$3,466,000	+5	-$ 931,000
Competing	2	100,000	18	952,000	18	942,000	--	- 10,000
Special	2	55,000	3	85,000	3	85,000	--	--
Subtotal	49	4,552,000	66	5,434,000	71	4,493,000	+5	- 941,000
Fellowships	7	357,000	12	391,000	23	507,000	+11	+ 116,000
Training Grants	6	539,000	6	539,000	2	141,000	-4	- 398,000
Research & Development Contracts	1	197,000	1	197,000	1	91,000	--	- 106,000
Total		$5,645,000		$6,561,000		$5,232,000		-$1,329,000

Glaucoma

Introduction

Glaucoma is one of the leading causes of visual disability in the Nation. It is responsible for twelve percent of all blindness in the United States and 14% of all new cases of blindness.

Glaucoma results when an obstruction in the outflow of a fluid, aqueous humor, leads to increased pressure within the eye with subsequent damage to the optic nerve and loss of vision. Progress toward preventing glaucoma has been delayed by the lack of an appropriate animal model for the disease, but NEI scientists have now developed a method for inducing changes in the eye of the rhesus monkey that closely resemble those observed in chronic, open-angle glaucoma in humans.

The NEI glaucoma program is placing particular emphasis on two main areas: early diagnosis and further development of new methods of treatment. In an effort to understand how elevated pressure within the eye causes destruction of the optic nerve, the Institute is supporting studies aimed at better understanding the relationship of changes in the circulation of blood to various levels of intraocular pressure. Knowledge gained in this study may help make possible the treatment of glaucoma based on changes in the eye's circulatory system before there is damage to the optic nerve.

New methods for treating glaucoma are also being explored. Such research is aimed at making therapy more efficient and easier for the patient.

Financing

This program is funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Program Plans for 1977: Studies of how increased pressure within the eye damages visual function will be conducted and research designed to identify more accurately the individuals at risk to closed-angle glaucoma will also receive emphasis.

Under the requested level approximately 68 research grants, of which 18 are new and competing will be awarded to address the needs and opportunities presented above. Additionally, 23 fellowships, 2 training grants, and 1 research contract will be awarded.

Sensory-Motor Disorders and Rehabilitation

Authorizing Legislation: Public Health Service Act, Title IV, Part F and I

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research Grants:								
Regular:								
Noncompeting	111	$4,904,000	111	$4,904,000	118	$6,453,000	+7	+$1,549,000
Competing	24	1,243,000	42	2,237,000	12	643,000	-30	- 1,594,000
Special	7	173,000	7	173,000	7	173,000	--	--
Subtotal	142	6,320,000	160	7,314,000	137	7,269,000	-23	- 45,000
Fellowships	40	862,000	49	1,091,000	19	417,000	-30	- 674,000
Training Grants	1	119,000	1	119,000	3	265,000	+2	+ 146,000
Research & Development Contracts	--	--	--	--	--	--	--	--
Total		$7,301,000		$8,524,000		$7,951,000		-$ 573,000

Sensory-Motor Disorders and Rehabilitation

Introduction

Sensory and motor disorders of vision may be either congenital or acquired and account for 16% of all blindness. Research into the visual system in health and disease is hoped to improve the diagnosis and treatment of strabismus (crosseye), amblyopia (decreased vision without apparent organic cause), and other sensory and motor problems. A total of 37,000 Americans are blind from optic nerve atrophy and myopia alone (9.2% of all legal blindness) and each year 3,000 more people are blinded by this disorder.

Basic research is being supported to elucidate the brain's role in the pattern of electrical impulses transmitted by the optic nerve from the retina and in feeding essential information back to the ocular muscles. These studies are exploring the development of visual capacity in the infant as well as normal visual function in the adult. In many cases, early detection of sensory and motor disorders may permit successful treatment; research is being pursued to facilitate this accomplishment.

Some of the other NEI-fostered investigations of sensory and motor disorders aim at a better understanding of the genetic and environmental factors involved in the development of the visual system, the neurologic aspects of oculomotor control, and refractive errors, including myopia (near-sightedness).

Financing

This program is funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Program Plans for 1977: Studies of strabismus, amblyopia, and disorders of the oculomotor muscles, and research leading to the prevention of degenerative, high myopia which endangers sight will be augmented. The Institute will also pursue additional research on the structure and function of the visual pathways from the retina to the brain and the correlation of these mechanisms with psychophysical functions and the processes of vision.

Under the requested level approximately 130 research grants, of which 22 are new and competing will be awarded to address the needs and opportunities presented above. Additionally, 19 fellowships, and 3 training grants will be awarded.

Intramural Research and Direct Operations

Authorizing Legislation: Public Health Service Act, Title IV, Part F

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Intramural Research.....	84	$5,295,000	89	$5,166,000	84	$5,835,000	-5	+$669,000
Direct Operations.....	54	2,530,000	60	2,476,000	54	2,602,000	-6	+ 126,000
Total	138	$7,825,000	149	$7,642,000	138	$8,437,000	-11	+$795,000

Intramural Research and Direct Operations

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. Activities of this area are carried out under the Clinical Branch which translates research findings into practical applications and the Laboratory of Vision Research which conducts basic research that will provide better insight into disease processes and the function of visual systems.

The direct operations activity of the National Eye Institute provides support for the overall administrative management and scientific direction of National Eye Institute programs. Included here is 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, and the Office of Scientific Reports and Program Planning. Additionally, funds are provided for salaries and other expenses of the Office of the Associate Director for Extramural and Collaborative Programs.

Program Plans for 1977: Investigations planned in the Clinical Branch were chosen to fulfill the commitment of the National Eye Institute to research in the major causes of blinding and disabling visual diseases. Therefore, the glaucoma research program will be continued, with emphasis on the action of drugs affecting intraocular pressure, and the effects of chronic administration of drugs under clinical conditions which may be useful in the treatment of glaucoma; mechanisms by which functionally independent drugs influence the rate of production of aqueous humor will be continued in primates and in isolated eyes; new drugs affecting the transport systems responsible for the composition of aqueous humor will be investigated; and the studies of the relationship of ocular hypertension and its treatment to the development of simple glaucoma will be continued. These experiments furnish the background for the application of this treatment method to human eyes having simple glaucoma. Research plans for the testing of three different surgical treatments for hemorrhagic glaucoma will be actively pursued. The study of vitrectomy as a treatment for vitreous hemorrhage in diabetic patients will be continued.

The Laboratory of Vision Research will continue to develop areas of research that will provide better understanding of disease processes and the function of visual systems. One of the major problems is the dystrophic process involving the retina. To aid in this study the process by which light is captured by the visual pigments and the various chemical transformations they undergo will be studied in normal and diseased retinas. The dangers of bright light on the retina will be evaluated further. In addition, research into cataracts will continue and a new experimental model for the study of congenital cataracts will be further explored.

The Office of Scientific Reports and Program Planning will continue to engage in activities designed to enhance communications with the biochemical scientific community and the general public. Initial responses and changing requirements based on the NEI's Vision Research Program Planning Report will be considered and updated. In this regard, program planning, analysis and evaluation activities will continue to receive emphasis. A collaborative controlled clinical trial to evaluate early vitrectomy will be monitored by the Office of Biometry and Epidemiology and Field Studies. This office will provide administrative, statistical and epidemiological planning and consultation.

The program planning and evaluation effort for vision research will continue with emphasis on implementing earlier guidelines and delineating a possible expanded role for the National Eye Institute in the health care system. There will be a final report on these latest planning efforts published in FY 1977.

Program Management

Authorizing Legislation: Public Health Service Act, Title IV, Part F

	1976 Revised President's Budget		1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Program Management	3	$171,000	3	$171,000	3	$180,000	--	+$9,000

Program Management

The Office of the Director of the National Eye Institute leads this activity which is the focal point from which decisions are made in regards to the scientific and administrative direction of Institute programs. During this fiscal year, this Office will be heavily involved in implementing the Vision Research Program Plan which was completed by a subcommittee of the National Advisory Eye Council in FY 1976. Efforts will be expanded in providing a sound scientific basis for alleviating the deprivation associated with impaired eyesight and blindness. In FY 1977, the program planning and evaluating effort for vision research will be continued by this Office with emphasis on implementing earlier guidelines and delineating a possible expanded role for the National Eye Institute in the health care system. A final report on the National Eye Institute's latest planning efforts will be published in FY 1977. In addition, this Office will continue the U.S. - Japan study initiated in FY 1976.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$16,215,000	Indefinite	--	$15,565,000

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 funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Accomplishments, 1976: A new photographic technique has been developed to facilitate diagnosis of certain retinal diseases, and may ultimately lead to improved methods of treating and perhaps even preventing these disorders. By employing two different dyes (fluorescein and indocyanine green), with specially equipped cameras, investigators can now tract simultaneous passage of blood through the interrelated circulatory systems of the retina and underlying choroid. The scientists hope the new technique will provide information about the interaction of the two circulatory systems in diseases such as diabetic retinopathy, macular degeneration, and sickle cell retinopathy. Additionally, they hope to learn how changes in blood flow might lead to visual loss associated with these disorders. Diagnosis of many retinal diseases has been complicated by their apparent similarity and by the lack of differential tests to distinguish among them. Knowledge gained from these studies may help in the development of improved methods for diagnosing, treating, and eventually even preventing these retinal diseases.

Objectives, 1977: Additional research will be supported on the pigment epithelium, a one-cell thick layer of tissue behind the retina, because of the basic relationship of this tissue to normal retinal function, and its potential importance in such visual disorders as retinitis pigmentosa, macular degeneration, and retinal detachment. Other studies will focus on how the retina is organized for the complex processing of visual information, the role of blood flow in the retina and underlying choroid in retinal degenerative and vascular disorders, the development of animal models for inflammatory diseases of the choroid and retina, correlations between clinical observation and laboratory analysis of diseased retinal and choroidal tissue and clinical research.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Corneal Diseases
(Public Health Service Act, Title IV, Parts F and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$6,890,000	Indefinite	--	$5,745,000

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 funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Accomplishments, 1976: Transplantation of the cornea may soon become more successful and its benefits extended to more people because of a new method for preserving the life of fresh donor tissue. During the past year, NEI-supported investigators developed an improved method for storing donor corneas that reduces the risk of graft failure and extends the survival period of healthy donor tissue from the traditional 48 hours to one week. This method involves bathing and immersing donor corneas in an inexpensive, easy-to-prepare solution. Tissues can be stored and even shipped in the medium for later transplantation. But the main advantage of the technique is that it preserves a vital layer of the cornea, the endothelial cells,which removes water from the tissue and are necessary for maintaining its transparency. The method is now being used by eye banks across the country to preserve donor corneas for transplantation, and some medical centers are even using the medium to prepare fresh tissue for immediate transplantation in order to preserve the endothelial cells. Further work is underway and the investigators believe their technique may be applied to the development of new means of storing other body organs and tissues to be used in transplantation.

Objectives, 1977: Tissue culture and biochemical analysis of abnormal human corneal tissue removed at the time of corneal transplantation will be pursued in order to learn more about corneal diseases in humans. Major problems related to increasing the success rate of corneal grafts will be addressed.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Cataract
(Public Health Service Act, Title IV, Parts F and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$4,282,000	Indefinite	--	$3,840,000

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 funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Accomplishments, 1976: Studies during the past year indicate that an interaction between protein and calcium may be responsible for the formation of the most common type of cataract, that associated with aging. This work may lead to a non-surgical means of treatment or even a means of preventing this major cause of blindness. Biochemical investigations conducted by NEI-supported scientists are providing new leads for better understanding how lens transparency is normally maintained and elucidating the process leading to cataract formation. Their studies have shown that the size and shape of lens proteins are important factors in determining lens transparency. In particular they have found that clumping of lens protein causes scattering of light and leads to loss of lens tranparency. As to the cause of the protein clumping they believe that high concentrations of calcium interact with lens protein to cause formation of the clumps. If this theory proves to be accurate, it may be possible to identify means of controlling the calcium and inhibiting the clumping process, thereby slowing down cataract formation.

Objectives, 1977: Investigations on the biological processes for maintaining normal lens hydration will be conducted to determine how aberrations in these mechanisms lead to cataract. Studies of protein changes in the lens in the development of senile cataracts will also be conducted. The search for new animal models for studying congenital cataracts will be intensified. Additionally, studies to find alternate methods for optical rehabilitation of cataract patients will be conducted.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Glaucoma
(Public Health Service Act, Title IV, Parts F and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$6,561,000	Indefinite	--	$5,232,000

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 funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Accomplishments, 1976: A new laboratory test has provided the first evidence of a cellular basis for glaucoma. NEI-supported investigations have shown that blood lymphocytes from people who have primary open-angle glaucoma and from those who show a marked ocular response to steroids are more sensitive to the action of the drug than other people. This is the first demonstration of a differential sensitivity of the eye to corticosteroids. The use of steroid eye drops in patients with this disease can cause marked elevation of intraocular pressure. In addition, prolonged administration of the drugs to some people without glaucoma can produce symptoms similar to the disease including irreversible visual loss. A high correlation was found between varying degrees of corticosteroid sensitivity in lymphocytes and the ocular response to steroid eye drops in a large group of patients. The lymphocyte test is not able to distinquish a person with diagnosed glaucoma from one who merely has an ocular response to topic steroids. However, the lymphocyte test performed in the test tube without need for administering steroid drugs offers significant advantages for studying the cellular basis of elevated intraocular pressure. Such information could lead to development of new drugs which may be effective in treating or even preventing this disease.

Objectives, 1977: Studies of how increased pressure within the eye damages visual function will be conducted and research designed to identify more accurately the individuals at risk to closed-angle glaucoma will also receive emphasis.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Sensory-Motor Disorders and Rehabilitation
(Public Health Service Act, Title IV, Parts F and I)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$8,524,000	Indefinite	--	$7,951,000

Purpose: The sensory 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 funded through the award of research grants and contracts, complemented by an intramural research program. Also fellowships and traineeships are awarded under the National Research Service Awards Act.

Accomplishments, 1976: New findings by investigators provide conclusive evidence that visual deprivation early in life can adversely affect the full maturation and proper functioning of the visual nervous system. These studies may lead to a more complete understanding of those factors involved in amblyopia (visual loss associated with disuse of one eye), strabismus (misalignment of the eyes), and other important causes of childhood visual disability and blindness. The investigators have shown that while the structure and function of the visual cortex is genetically determined and present at birth, environmental factors are important in shaping the brain's response to visual stimulation. Animal studies showed that the normal visual cortex contains functional systems, parallel sheets of cells, specific to a particular eye or type of visual stimulus. Visual deprivation early in life can result in loss of cells and cause a functional system to shrink in width thus interfering with normal development of the visual nervous system. Their findings substantiate the theory that the visual system is flexible and that proper stimulation early in life is important to its full development.

Objectives, 1977: Studies of strabismus, amblyopia, and disorders of the oculomotor muscles, and research leading to the prevention of degenerative, high myopia which endangers sight will be augmented. The Institute will also pursue additional research on the structure and function of the visual pathways from the retina to the brain and the correlation of these mechanisms with psychophysical functions and the processes of vision.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Intramural Research and Direct Operations

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
149	$7,642,000	Indefinite	138	$8,437,000

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. The direct operations activity of the National Eye Institute provides support for the overall administrative management and scientific direction of National Eye Institute programs. Included here is the Office of Biometry, Epidemiology and Field Studies, and funds for salaries and other expenses of the Office of the Associate Director for Extramural and Collaborative Programs.

Explanation: The Institute's Intramural research program is comprised of a Laboratory of Vision Research and a Clinical Branch. The direct operations activity consists of the Office of Biometry, Epidemiology and Field Studies, and the Office of the Associate Director for Extramural and Collaborative Programs.

Accomplishments in 1976: Biochemical and immunological studies were conducted by the Intramural research program to determine if specific protein antigens in the cornea were responsible for cornea graft rejections; follow-up experiments for effecting delay or prevention of cataracts were explored; the problem of new vessel formation was aggressively pursued utilizing the new surgical procedure of vitrectomy. The Office of Biometry and Epidemiology coordinated a large scale clinical trial in vitrectomy, and continued to gather national statistics on the incidence and prevalence of eye diseases. The Office of Extramural and Collaborative Programs continued its evaluation of NEI programs utilizing the computer mechanism.

Objectives for 1977: The glaucoma research program will be continued, with emphasis on the action of drugs affecting intraocular pressure, and the effects of chronic administration of drugs under clinical conditions which may be useful in the treatment of glaucoma; mechanisms by which functionally independent drugs influence the rate of production of aqueous humor will be continued in primates and in isolated eyes; new drugs affecting the transport systems responsible for the composition of the aqueous humor will be investigated; and the studies of the relationship of ocular hypertension and its treatment to the development of simple glaucoma will be continued. Research plans for the testing of three different surgical treatments for hemorrhagic glaucoma will be actively pursued. The study of vitrectomy as a treatment for vitreous hemorrhage in diabetic patients will be continued. The process by which light is captured by visual pigments and the various chemical transformations they undergo will be studied in normal and diseased retinas. The dangers of bright light on the retina will be evaluated further. In addition, research into cataracts will continue and a new experimental model for the study of congenital cataracts will be further explored.

The Office of Scientific Reports and Program Planning will continue to engage in activities designed to enhance communications with the biomedical scientific community and the general public. Initial responses and changing requirements based on the NEI's Vision Research Program Planning Report will be consolidated and updated. In this regard, program planning, analysis and evaluation activities will continue to receive emphasis. A collaborative controlled clinical trial to evaluate early vitrectomy will be monitored by the Office of Biometry and Epidemiology and Field Studies. This office will provide administrative, statistical and epidemiological planning and consultation.

The program planning and evaluation effort for vision research will continue with emphasis on implementing earlier guidelines and delineating a possible expanded role for the National Eye Institute in the health care system. There will be a final report on these latest planning efforts published in FY 1977.

NATIONAL INSTITUTES OF HEALTH

National Eye Institute

Program Purpose and Accomplishments

Activity: Program Management
(Public Health Service Act, Title IV, Parts F)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
3	$171,000	Indefinite	3	$180,000

Purpose: The Office of the Director serves as the focal point for the scientific and administrative direction of Institute programs.

Explanation: This activity consists of the Office of the Director, National Eye Institute and his immediate support staff.

Accomplishments in 1976: The Vision Research Program Planning Report was completed in conjunction with the National Advisory Eye Council. This plan identified needs and opportunities where significant research advances in vision research could be expected in the near future.

Objectives for 1977: The program planning and evaluation effort for vision research will be continued with emphasis on implementing earlier guidelines and delineating a possible expanded role for the National Eye Institute in the health care system. A final report will be published during 1977.

Transition Quarter Analysis

	Budget Authority by Activity			
	1976 Estimate		Transition Quarter	
	Pos.	Amount	Pos.	Amount
Retinal and Choroidal Diseases	--	$16,215,000	--	$3,016,000
Corneal Diseases	--	6,890,000	--	1,310,000
Cataract	--	4,282,000	--	773,000
Glaucoma	--	6,561,000	--	1,296,000
Sensory-Motor Disorders and Rehabilitation	--	8,524,000	--	1,495,000
Intramural Research and Direct Operations	149	7,569,000	149	1,867,000
Standard Level Users Charge		73,000		--
Program Management	3	171,000	3	43,000
Total, obligations	152	50,285,000	152	9,800,000

Explanation

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.

TUESDAY, MARCH 2, 1976.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

WITNESSES

DR. DAVID P. RALL, DIRECTOR
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. RONALD W. LAMONT-HAVERS, DEPUTY DIRECTOR, 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
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We are continuing with the National Institutes of Health. We will now 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.

[Dr. Rall's biographical sketch follows:]

Name: David P. Rall, M.D., Ph. D.

Position: Director, National Institute of Environmental Health Sciences, Assistant Surgeon General, Public Health Service.

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.

Intern, second (Cornell) medical division, Bellevue Hospital, 1952–53.

Research associate in pharmacology, Northwestern University, 1950.

Assistant in pharmacology, Northwestern University, 1949–50.

Baxter fellow in pharmacology, Northwestern University, 1947–49.

Association memberships: American Association for the 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; Society of Toxicology; Washington Academy of Sciences; Society for Occupational and Environmental Health; and American College of Preventive Medicine.

Special awards, citations, or publications: Member, National Academy of Sciences/National Research Council Safe Drinking Water Committee, 1975–present.

Member, Secretary's Review Panel on New Drug Regulation, 1975–present.
Associate Editor, Journal of Toxicology and Environmental Health, 1974–present.
Editorial Board, Archives of Environmental Health, 1973–1976.
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.
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 Research, 1970–74.
Chairman, HEW Departmental Committee on Drug Research and Regulations, 1970.
Editorial board, Pharmacological Reviews, 1969–72.
Chairman, National Institute of General Medical Sciences Pharmacology-Toxicology Review Committee, 1967–69.
Member, Graduate Council, George Washington University, 1962–71.
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. You have some people with you.

Dr. RALL. Yes. I would like to introduce on my far left Mrs. Peggy McKinney, our budget officer, and on my immediate left Mr. George Kingman, our executive officer.

Mr. FLOOD. I see you have a prepared statement. How do you want to handle that?

Dr. RALL. We worked very hard to keep this statement short. It's my impression that when you summarize a statement orally it tends to take longer than if you just read the statement. I will do whichever you prefer.

Mr. FLOOD. It is your show.

Dr. RALL. Let me read it, then.

STATEMENT BY THE DIRECTOR

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 and discuss our budget request for the coming year. This is, for us, a landmark occasion: This budget, which I am pleased to present, is the 10th budget for the NIEHS and it represents recognition on the part of the administration of the importance of this area of research.

The definition of the field of environmental health is complex; yet the guiding precepts in our national health programs are simple: Environmental factors can and do cause human disease, and research can and will decrease human disease.

NEEDS FOR ENVIRONMENTAL HEALTH RESEARCH

Intrinsic to our modern civilization are a great many economic and social forces and technological developments which constantly increase the need for research efforts in environmental health. Paramount

among these is the development of a sophisticated, complex chemical process industry which is involved in the production of totally new and unique chemical compounds to which man has never before been exposed. We are concerned that these compounds may add a new burden of human disease, disability, and death.

A second major factor increasing the need for research efforts in environmental health is our constantly increasing demand for energy. Critical health (including genetic) problems can stem from sulfur oxides and particulates in the air, nitrogen oxide from powerplants and automobiles, hydrocarbons from coal liquification or gasification, or oil spills in the ocean and heavy metals of known and serious toxicity.

A third factor, perhaps more subtle than the others, is the constantly increasing urbanization of modern civilization which leads to the concentration of pollutants in densely populated cities and industrial centers.

Although we all enjoy the fruits of modern civilization we must now face the problems arising from growing and largely uncontrolled concentrations of toxic pollutants in all sectors of our environment.

NEEDS IN ENVIRONMENTAL HEALTH RESEARCH

"How can we prevent the disease, disability, and death caused by the increasing numbers of toxic environmental agents?" We believe that research can accomplish this goal, either directly through restricting human exposure, or indirectly through understanding the whys and hows of damage or possible treatment of such damage. Although now and for the future the direct route will be important and often essential, the indirect route will assume increasing importance.

Proscription or restriction of exposure to pollutants and chemicals can cause serious economic disruption. Some toxic agents yield very real benefits. Thousands of compounds to which man is now exposed have never been adequately tested for toxicity; and to do so with current methods would require vast sums. If we develop an understanding of how agents exert their toxic effects, then we may be able to predict which agents can cause toxic effects and to test these intensively before they become widespread.

No example illustrates these problems better than the polychlorinated biphenyls (PCB's), which I have often discussed before this committee. These heat resistant, electrical insulating fluids were the subject of a meeting held by our Institute in December 1971. Scientists from all over the world participated in the conference and expressed their strong concern that adverse human health effects would be likely if PCB's were not carefully controlled.

HEW research has now confirmed this concern. Dr. Kimbrough of the Center for Disease Control recently reported that long-term studies indicated a carcinogenic effect in rats from PCB's. NIEHS grantees have shown that PCB's at low concentrations seriously affect reproduction in the rhesus monkey; also NIEHS scientists have shown how persistent PCB's are in experimental animals and in marine species. They also have shown how these agents are metabolized by the body and converted into different compounds; and this may help to explain their carcinogenicity.

Public concern was again heightened when fish in the Great Lakes and the Hudson River were recently found to contain dangerous levels

of PCB's. This occurred even though the U.S. manufacturer of PCB's restricted their use. Thus, failure to reduce PCB contamination when the problem first became evident has now resulted in an additional health hazard, the resolution of which will cause severe economic hardship on Great Lake and Hudson River fisheries.

Let me add, that since this statement was written the State of New York has closed the Hudson River to commercial fishing and urged that sport fishermen not eat their catch but throw it back.

NIEHS PROGRESS AND GOALS

During the remainder of my testimony I would like to describe for you some of the progress we have made.

Last year I told you that NIEHS researchers had developed a mouse model of the toxic effects of the synthetic estrogen diethylstilbestrol (DES) which is currently used as a "morning after" contraceptive and as an animal feed additive to speed weight gain. In addition to well-known effects on female offspring of DES-treated mothers, our scientists found male mouse offspring are sterile and have other reproductive tract abnormalities following prenatal exposure to DES. Now physicians at a Chicago hospital have reported similar effects in human male offspring of DES exposed mothers.

By use of other newly-developed techniques and models, some pesticides have been found to disrupt nerve function and to influence behavior and learning patterns. The human toxicity following accidental, chronic exposure to the pesticide Kepone in Hopewell, Va., has resulted in over 20 victims being hospitalized at one time or another for such problems as apparent brain and liver damage, sterility, slurred speech and loss of memory. There is no known treatment for these patients. To develop effective treatment methods we need information regarding the mechanism of Kepone toxicity and its persistence within the body. We have recently awarded a research contract to physicians at the Medical College of Virginia who are taking care of these patients, to develop this information.

Strong evidence has been uncovered by various NIEHS grantees which indicates ozone and nitrogen dioxide are contributing, if not primary, causes of pulmonary emphysema and chronic nonspecific pulmonary disease. Within a few hours of exposure to less than 0.5 part per million ozone (a concentration readily achieved at peak traffic hours in some urban areas), considerable toxic reaction in the lung becomes apparent. Other grantees have found that the damage in the rat after exposure to ozone occurs in the small airways of the lung.

While these studies have established what happens in ozone and nitrogen dioxide induced lung disease, the research of other NIEHS grantees has encouraged the belief that much of the lung damage and emphysema induced by these two pollutants at low levels may be prevented and perhaps reversed in the early stages. NIEHS grantees have demonstrated that some lipid antioxidants, particularly vitamins A and E, and certain minerals, particularly zinc, can protect against ozone-induced emphysema and lung toxicity. Emphysema has led to death for an increasing number of people

since 1950, and chronic nonspecific pulmonary disease has become a leading cause of disability among adult males. Evaluations must now be made of vitamins A and E, zinc, and other compounds—as well as combinations of these—first in test animals and, if successful, eventually human populations at risk of toxic environmental exposure. An NIEHS-sponsored conference on pollutant-induced lung disease and its possible amelioration by vitamin therapy will be held Thursday and Friday of this week.

Our seven university-based environmental health sciences centers are national resources for research and information on problems in this area. In 1975 NIEHS center scientists were undertaking research supported by approximately 100 grants or contracts from other Federal agencies including EPA, NIOSH, FDA, and ERDA; and various industries, and public groups. Our center at Mount Sinai Hospital is a world focus for research and information on the effects of asbestos. Since I last described some of their work to you, scientists at this center have found that cancer of the lungs and a rare cancer (called mesothelioma) of the lung and abdominal linings occur more frequently in insulation workers and others in building trades who are exposed to relatively small amounts of asbestos. The Mount Sinai group has also discovered that spackling, patching, and taping compounds contain appreciable levels of asbestos minerals. Use of these compounds in home repair work may expose the user, and other members of the household, to concentrations of asbestos that may lead to disease. Similar hazards have also been found to exist in automobile brake repair shops where asbestos fibers are disseminated during installation of brake linings.

Our newest Environmental Health Sciences Center at the University of Rochester is investigating an emerging problem of methyl mercury contamination in two areas in Canada. The fish caught in these popular lakes contain the highest concentrations of methyl mercury yet recorded in North America. Levels of methyl mercury in blood taken from humans who eat these fish are in the same range as those reported for victims of the Japanese Minamata disaster. Clinical studies, as yet incomplete, suggest neurologic damage may be seen in people who ate these fish.

We are continuing work to determine the health consequences of: The industrial use of bis(chloromethyl) ether, earlier identified by our grantees as being a potent carcinogen; and the effects of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), a highly toxic contaminent of certain herbicides and other pesticides, which our scientists earlier showed affects the development and viability of mouse and rat fetuses and have recently found increases the susceptibility in mice to infection.

SUMMARY

One of the major themes in this year's forward plan for health is preventive medicine, which we believe to be the best and cheapest medicine in the long run in terms of dollars expended and human misery prevented. The American Medical Association recently estimated, for example, that at today's hospital costs the Nation saves $2 billion per year because of the vaccine developed against poliomyelitis. A key element to preventive medicine in the environmental health field is pre-

venting exposure of segments of the population to disease-producing substances. We can only prevent such exposure when we have the tools needed to identify toxic agents and determine how toxic effects are exerted. The National Institute of Environmental Health Sciences is committed to developing this information.

In conclusion, Mr. Chairman, the budget request for the National Institute of Environmental Health Sciences for 1977 is $46,141,000. I shall be pleased to answer any questions you may have.

Mr. FLOOD. Doctor, when you were here last year you were wearing a belt that had a message on it. As I recall, the message was NIEHS needs money and positions.

What are you wearing this year?

Dr. RALL. The same belt.

Mr. FLOOD. With that 22-percent increase you received I thought you would be wearing a smile this morning.

Dr. RALL. I am also wearing a smile this morning.

INCREASE FOR 1977

Mr. FLOOD. The 1977 budget for the National Institute of Environmental Health Sciences calls for an $8 million increase. How do you plan to use the increase? Tell us the specific areas.

Dr. RALL. We are going to use this increase in most of our major areas of research concern. For example, the largest percentage increase will be in environmental mutagenesis and reproductive toxicology, which will be an increase of $1.8 million, about an 80-percent increase in that program. We are, as you know, deeply concerned about the possible genetic effects of mutants in our environment. We are developing methods to test for such genetic effects. We are concerned about the effects on the developing fetus and the problems of stillborns and malformed babies.

We are developing better test methods, and we are studying compounds in this area. This is the largest percentage increase. It is still a small program. We are developing it as rapidly as we think we can.

POSITION REDUCTION

Mr. FLOOD. I notice that with an $8.3 million increase you show a reduction of 33 positions for your intramural research activities. What are you doing? Are you emphasizing the grant and contract programs as opposed to the development of strong intramural research programs?

Dr. RALL. We would like to develop both hand in hand because I think they work very well together. It is my understanding that those 33 positions will likely be restored, and we will be able to fill those before the end of the fiscal year.

Mr. MILLER. I understand that came up yesterday too, Mr. Chairman. That has to do with 1977. As you know, we have provided the full authorization in the 1976 appropriation, but we don't have any guarantees concerning those positions in 1977.

Mr. FLOOD. Were those positions added by this committee ever allocated to you by OMB?

Dr. RALL. Not yet.

Mr. MILLER. We allocated them to each of the agencies in HEW by memorandum last Friday.

Mr. FLOOD. All right.

ENVIRONMENTAL MUTAGENESIS

Doctor, this committee added $1,500,000 to your intramural research budget last year for the purpose of expanding the environmental mutagenesis program you touched on previously and for other activities in your Institute. Did you comply with that directive? It was a directive?

Dr. RALL. We found it difficult to comply with that directive until we had the positions allocated.

Mr. FLOOD. Give us some examples if you complied at all.

Dr. RALL. We are now in the process of recruiting, assuming the additional ceilings arrive, scientists to strengthen our mutagenesis program, to strengthen our epidemiology program, and begin an initial effort at developing a behavioral toxicology program. This latter is very important.

The term "behavioral toxicology" is a way of trying to say we are concerned that during the reproductive process, exposure to chemicals can cause newborns to be deficient in sensory, motor, and intellectual capabilities, and we think it is important to develop test methods to determine if that is true.

The standard anatomic methods are relatively crude and we want to develop methods of behavioral testing. Can they run a maze as well as their normal counterparts?

Mr. FLOOD. That is an example of your compliance with the directive?

Dr. RALL. Yes.

ENERGY

Mr. FLOOD. I know you are conducting research on the health effects of exposure to sulphur oxides, heavy metals, hydrocarbons, gasification of coal.

Is EPA or ERDA conducting any related research on the pollution that I have just mentioned here?

Dr. RALL. Yes, there is an interagency group, which consists of NIEHS, NIOSH, EPA, and ERDA, which is working on the health effects of new energy sources and expanded old energy sources.

Mr. FLOOD. How does their work differ from yours?

Dr. RALL. This interagency group meets together often and we have parceled out who does what research task. We decided to document this in a report, the King/Muir report, as to who ought to do what, because this is an enormous task. We have been working together since then. I could submit for the record the details of how we are doing this and ERDA is doing that.

Mr. FLOOD. All right. That will be a good answer.

[The information follows:]

INTERAGENCY ENERGY-RELATED HEALTH EFFECTS RESEARCH

During the summer and fall of 1974, an interagency task group met to identify needed research on the potential adverse health and environmental problems associated with energy use. As part of the report of the Interagency Working Group on Health and Environmental Effects of Energy Use—the King/Muir report—published in November 1974, the health subgroup—consisting of

representatives from NIEHS, NIOSH, ERDA, and EPA—recommended that research be pursued on five objectives:

Objective 1.—To identify hazardous agents associated with energy technologies.

Objective 2.—To develop more sensitive and rapid biological methods to evaluate dose and damage to man.

Objective 3.—To determine the metabolism and fate of hazardous agents associated with energy technologies.

Objective 4.—To evaluate the short-term and long-term hazards of exposure of normal, susceptible ,and stressed population groups to different levels and combinations of bilologically active agents associated with energy technologies.

Objective 5.—To determine the processes of damage, repair, recovery, protection, and amelioration of biological systems exposed to hazardous agents associated with energy technologies.

The King/Muir report recommended specific projects and tasks to accomplish these objectives and identified agencies to be responsible for the pursuit of the projects and tasks. Of approximately $78 million in new funds appropriated to support research on the health and environmental aspects of energy, $20 million was allocated for research on health problems, the remainder being divided among research efforts on ecological effects; pollutant characterization, measurement and monitoring; environmental transport processes; and integrated assessment. These funds were appropriated to EPA for passthrough to other agencies in support of the objectives of the King/Muir report. NIEHS received $3.6 million from EPA to support new research on energy-related health problems, adding to approximately $10 million in ongoing energy-related health research.

In October 1975 the Energy Research and Development Administration—ERDA—published its first annual "Federal Inventory of Energy-Related Biomedical and Environmental Research for Fiscal Year 1974 and Fiscal Year 1975" (ERDA–110). This report, developed from input provided by NIEHS and other agencies, assessed the support allocated to accomplish the objectives of the King/Muir report—including a catchall objective 6—from both base and passthrough programs. The amounts spent under each of the objectives are indicated in the attached table 3c from ERDA–110.

The ERDA report also identified the energy technologies addressed by the different King/Muir objectives and the resources allocated toward research on health problems associated with each. This distribution is shown in table 5c from ERDA–110, attached.

In addition to periodic meetings of administrative staff coordinating energy-related health research projects for NIEHS, NIOSH, EPA, and ERDA, these four agencies sponsored a 3-day retreat for scientists working on energy-related projects in early January 1976. This meeting, which was attended by about 160 scientists from all four agencies and from the industrial and university community, was called at the suggestion of NIEHS for the purpose of increasing communication between biomedical scientists concerned with the health effects of energy and recommending additional steps to deal with these problems.

TABLE 3c

RESEARCH OBJECTIVE VS FEDERAL AGENCY - FY 1975
RESEARCH CATEGORY: HEALTH EFFECTS

(DOLLARS IN MILLIONS)

AGENCY → / Objective Number** ↓	ERDA	EPA	TVA	NASA	DHEW		NSF	DEPT OF COMMERCE			DEPT OF INTERIOR					DEPT AGR.	DOD	TOTAL
					NIH	NIOSH		NOAA	OEA	NBS	BLM	OBS/FWS	USGS	BM	B. RECLAM			
1	1.130	4.006			0.154	0.047												5.337
2	2.085	3.090			2.817	0.079												8.071
3	4.302	1.004			2.141	0.543												7.990
4	44.666	6.706			8.310	1.891												61.573
5	20.116	0.924			4.208	0.816												26.064
6	4.376																	4.376
TOTAL	*76.675	15.730	-0-	-0-	17.630	3.376	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	113.411

*DOES NOT INCLUDE MEDICAL APPLICATIONS, EDUCATION, AND TRAINING.

**REFER TO KEY LIST ON FOLLOWING PAGE FOR DESCRIPTION OF OBJECTIVES.

TABLE 5c

ENERGY TECHNOLOGY CATEGORY VS FEDERAL AGENCY
RESEARCH CATEGORY: HEALTH EFFECTS
FY 1975

(DOLLARS IN MILLIONS)

AGENCY → / TECHNOLOGY ↓	ERDA	EPA	TVA	NASA	DHEW		NSF	DEPT OF COMMERCE			DEPT OF INTERIOR					DEPT AGR.	DOD	TOTAL
					NIH	NIOSH		NOAA	OEA	NBS	BLM	OBS/FWS	USGS	BM	B. RECLAM			
Coal	10.336	6.274			5.715	1.421												23.746
Oil and Gas		1.133			0.689	0.740												2.562
Shale	0.236	1.049			0.416	0.160												1.861
Geothermal		0.195			2.000													2.195
Nuclear	43.167	0.995			0.690	0.066												44.918
Solar	1.626				0.989													2.615
Hydroelectric																		
Conservation	1.746	0.200			1.182	0.409												3.537
Multi Technology	7.458	5.884			5.949	0.580												19.871
General Science	12.106																	12.106
TOTAL	*76.675	15.730	-0-	-0-	17.630	3.376	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	-0-	113.411

*DOES NOT INCLUDE MEDICAL APPLICATIONS, EDUCATION, AND TRAINING.

Mr. FLOOD. Do you have any idea how much EPA and ERDA will spend on health-related programs in fiscal 1977?

Dr. RALL. EPA, not just energy but total, about $25 million.

Mr. FLOOD. What about ERDA?

Dr. RALL. ERDA will spend something on the order of $80 million in health research, but a very large fraction of that is on the effects of ionizing radiation.

ENVIRONMENTAL HEALTH SCIENCES CENTERS

Mr. FLOOD. In your justification you mentioned that the grant-supported environmental health science centers provided outstanding capabilities in many, many areas. Can you give us some ideas of the work conducted at each center?

Dr. RALL. Certainly. I'll start with the two centers I discussed. The one run by Dr. Selikoff at Mt. Sinai, really knows more about asbestos and fine fibers than any other research group in the United States and probably the world.

They also have unique ability to find groups of people who have been exposed to all sorts of toxic agents and follow these people and determine what effects such agents have.

The newest center run by Dr. Clarkson at the University of Rochester has had an excellent record of studying heavy metals and in particular methyl mercury. They also have what for us is important, considerable capability in behavioral toxicology, so we look forward to working very closely with them.

In Boston Dr. Jim Whittenberger has a center at Harvard. This center does some of the best toxicology in the country. It is concerned about vinyl chloride and other vinyl chloride-related toxicity. It has a strong epidemiology component identifying groups of people who have had exposure to air pollutants and following them for long periods of time. There is an excellent group in lung pathology as related to environmental factors.

FOOD ADDITIVES

Mr. FLOOD. One of the things you mentioned in your justification is nutritional science. Can you elaborate on that capability? Are they concerned with artificial preservatives?

Dr. RALL. The program project at the Massachusetts Institute of Technology under Dr. Gerald Wogan has really been the one involved in food additives and their toxicity. They have been working in this area for many years.

Mr. FLOOD. On artificial preservatives?

Dr. RALL. Yes, and natural contaminants such as the mycotoxins.

NEW ENVIRONMENTAL HEALTH SCIENCES CENTER

Mr. FLOOD. You are proposing to initiate a new grant support in the environmental health sciences centers. Will you tell the committee what the emphasis has been at this center, what the emphasis will be, and why that is necessary?

Dr. RALL. We think the centers have worked very well in focusing on one major area. We have a number of possibilities for our next

center. It is unkown which we will pick. The free enterprise competition system works.

Mr. FLOOD. How will the work of your Center differ from the work being supported by the Heart and Lung Institute through its research and demonstration in pulmonary disease? I understand that particular center emphasizes research on the occupational pulmonary diseases which result from prolonged exposure to harmful dusts, fumes in various industries. It would look as though close coordination would be essential there.

Dr. RALL. It is essential and it happens. We are concerned with the environmental pollutant, how it gets to the cell, how it causes its damage. That encompasses our major interests.

The categorical Institute, such as the Heart and Lung, then is interested in what happens to the damaged cell, how the damage progresses and so forth. Obviously we work very closely together in this area. The heart and lung people just came down and visited us for 2 days a few months ago. We visit them when we come up to Washington. It is a good close coordination.

SHORT-TERM QUALITATIVE TESTING

Mr. FLOOD. Last year you recall we talked briefly about the need for short-term qualitative tests so that you can rapidly and intensively test these potential environmental hazards. What progress have you made in that area?

Dr. RALL. That research is going very well. It was really best illustrated at a meeting we held in Seattle in the United States-Japan program. The Japanese have been very vigorous in this area. Our American scientists and the Japanese scientists got together and compared their results, and it seems to me that the rapid test methods using bacteria and human cells in culture are at a stage where we ought to begin to use them as a screening method for the 10,000 or 15,000 environmental chemicals.

Mr. FLOOD. If you were to perfect this short-term qualitative test, would that eliminate the need for doing further testing in animals?

Dr. RALL. No, I don't think it will eliminate the need. What it will do is let us take our limited capabilities for the long-term intensive testing and apply them to those compounds that are most likely to cause toxicity, the ones we are most intensively exposed to.

We can use the short-term tests to screen out of the large universe of compounds those which ought to be intensively studied. So what I think it will do is make the system more efficient.

MERCURY AND LEAD

Mr. FLOOD. Also in your justification you state that long-term exposure to mercury and lead has an adverse effect upon learning behavior. Can you elaborate on that and tell us what specific work are you into?

Dr. RALL. I can give you work we are supporting by grants, but this is one of the areas we feel we have to get into in our intramural laboratories. If you give to pregnant sheep enough lead to cause a blood lead level about the same as is present in many of our inner city

dwellers, those sheep deliver the lambs, then you test the lambs for ability to learn, to discriminate between a triangle and a circle, or walk a maze, and it is found that those lambs that came from lead-treated mothers can not learn as well. This is the sort of thing that worries us very much. This is a preliminary experiment. We do need to do this with other species, other heavy metals, and get a much better idea of what could also destroy learning ability.

ASBESTOS

Mr. FLOOD. Last year the committee gave you $1 million to continue the study of the effects of orally ingested asbestos. What have you learned from that contract?

Dr. RALL. We have two very large contracts in this area; one to look at the response in the hamster and the other in rats. We have not actually put the first animal on asbestos yet. That will happen very shortly.

We are accumulating the supplies of asbestos needed for the studies, and this we think is absolutely critical, that we have a well-defined sample of asbestos that is well characterized and that we obtain enough of it so that in future years it will become a reference sample.

Asbestos is probably a weak carcinogen and often its carcinogenic effect is expressed when other carcinogens are present, so we are setting up a special study——

Mr. FLOOD. Have you concluded that?

Dr. RALL. I think if you look at Dr. Selikoff's data, the incidence of lung cancer in any but the heavily occupationally exposed people, is not very high.

Mr. OBEY. Would you yield on that for clarification?

Mr. FLOOD. Yes.

Mr. OBEY. When you say asbestos is probably a weak carcinogen, are you talking about its ingestion as opposed to breathing it?

Dr. RALL. We don't know about its ingestion yet.

Mr. OBEY. You are talking then of airborn?

Dr. RALL. Yes. For instance, men exposed all their lives to heavy amounts will not get lung carcinoma in greatly excess amounts unless they also smoke. It acts in many ways like a cocarcinogen, which, if there is another carcinogenic substance present, instead of having a small effect, will suddenly have a very large effect. So this is another part of this study that we have begun.

EPIDEMIOLOGIC STUDIES—CDC

Mr. FLOOD. The Center for Disease Control supports surveillance epidemiologic studies of birth defects. How do you use the information that they produce?

Dr. RALL. We have a relationship where we feed information back and forth on that. By the same token, we give them clues of experiments in animals which suggest where they ought to look in their clinical studies.

TOXICITY OF PESTICIDES

Mr. FLOOD. Who has the responsibility for determining the toxicity of pesticides? Is that you or is that EPA?

Dr. RALL. That is the manufacturer in the current system. Under the Federal Insect and Rodenticide Act it is the manufacturers' responsibility to show that his compound is safe and effective.

Mr. FLOOD. Who determines the toxicity, you or EPA?

Dr. RALL. The manufacturer is supposed to do the work and then EPA, since it is the regulatory agency. They will say, "This was a good job; we will let you license it," or "This is a bad job; go back and do more."

KEPONE

Mr. FLOOD. Pesticides like Kepone get into the environment in these large amounts without anybody being aware that it is a health problem.

Dr. RALL. That was just a most distressing situation.

Mr. FLOOD. That is why I ask you.

Dr. RALL. I think it is clear from the testimony that a lot of people simply didn't follow it closely enough. Kepone was known to be very hazardous.

Mr. FLOOD. There are large amounts all over the area.

Dr. RALL. Most of it was shipped out of the United States. Almost none of it was used in the United States, and unfortuntaely I think this made people less concerned about it. If it had all been used in the United States, then there would be a much greater awareness by the regulatory agencies of its hazards. Since most of it was shipped away, I think the manufacturing process was not followed as closely as one would have liked.

Mr. FLOOD. Is there a systematic review of the most commonly used pesticides in terms of health effects?

Dr. RALL. Again, the insecticide law mandates a 5-year review of every pesticide, and that is within the province and perogative of the EPA.

ENVIRONMENTAL CANCER

Mr. FLOOD. We keep hearing statistics and statistics and more statistics, that 60 to 80 percent of all cancers are caused by environmental factors. Some people tell us those figures are very misleading. They tell us that a large number of these so-called environmental cancers are caused by voluntary acts—smoking, eating highly refined diets, and so forth—actions that the Federal Government can't do anything about. Do you agree with that?

Dr. RALL. Smoking is a voluntary act. Eating is kind of necessary in the long run.

Certainly some of that 60 to 80 percent falls in the voluntary sort of problem you describe, but there is an unknown but probably very large fraction of that, I am convinced, is due to a combination of chemicals in our air, in our water, in our food supply.

Mr. FLOOD. What is the answer?

Dr. RALL. There is no one answer.

Mr. FLOOD. Does it call for more health education?

Dr. RALL. I think more health education needs to be done.

Mr. FLOOD. Do you think enough is being done about health education?

Dr. RALL. I don't think I really can intelligently comment on whether enough is being done. Certainly health education would be important in this area. We need more research and more testing also. We need firm regulatory action.

Mr. FLOOD. If we were able to change people's eating habits, what reduction in the environmental cancers would the country experience?

Dr. RALL. I don't know any way of estimating that. There would be some.

MICROWAVES

Mr. FLOOD. Are you doing any research in this matter of microwaves?

Dr. RALL. Yes, we are.

Mr. FLOOD. What do we know about it?

Dr. RALL. Not as much as we ought to know about it. The microwave story is fascinating. The accepted safe level for microwave exposure is 10 milliwatts per square centimeter in the United States. The Russian standard is .01 milliwatts, a thousandfold lower. Now the Russians have done both long- and short-term experiments, but I would not call these every definitive. I am not convinced, after looking at the experimental data, that we have enough evidence to really say that their standard of .01 is real.

In the United States we are developing the sort of equipment that allows us to generate a constant known field of microwaves. We are doing this mostly in our own laboratories. We are beginning now to expose various tissues of animals to these.

We have found that if you use quail eggs which are very small—and this is important because we can evenly irradiate only a field about 15 inches in diameter—at somewhat over 10 milliwatts per square centimeter, we do get some minor effects in development of fertile quail eggs.

We have looked at the effect of microwaves on the spinal cord for nerve impulses passing up and down the spinal cord.

Mr. FLOOD. You haven't been involved in the situation in Moscow vis-a-vis our embassy?

Dr. RALL. No; I haven't.

COORDINATION—AGING INSTITUTE

Mr. FLOOD. In your justification you say, "Studies are underway currently to assess the long-term effects of heat stress, dehydration, and other physical factors of aging and degenerative diseases associated with aging."

Is this a collaborative research effort with the Aging Institute?

Dr. RALL. It will be because this is a program we have had going.

Mr. FLOOD. How would you coordinate with the Aging Institute?

Dr. RALL. The way we coordinate with other Institutes is through participation in the NIH Institute Director and Scientific Directors' meetings; serving on each other's expert committees; and through scientist-to-scientist collaboration and cooperation. As with the Heart and Lung Institute, we visit each other's laboratories for the purpose of maintaining current awareness of research planned and in progress.

EPIDEMIOLOGY

Mr. FLOOD. You also state in your justification that you plan to initiate a program of epidemiology. We all recognize that epidemiology is pretty important in any health research. Why, however, should we allow you to spend all this money on epidemiology when we are already investing a great deal of money for epidemiology at the Center for Disease Control, National Institute for Occupational Safety and Health, the National Center for Health Statistics, et cetera, so why?

Dr. RALL. The Center for Disease Control does not focus on chronic disease epidemiology, nor on the long-term relationship between chemical exposure and what happens to that group of people 20 years later. They are primarily focused on communicable diseases and very short-term effects. That has classically been their role for the 20 years they have been in existence.

NIOSH does a superb job with occupational effects but they are limited to occupational. The long-term exposure to populations, to families, to mothers, and so forth, is not their purview. We do work with them.

The National Center for Health Statistics does not really do epidemiology.

Mr. FLOOD. For the record, tell us, in detail, how your epidemiology studies are going to differ from the agencies that I have just mentioned, and clearly how are these programs going to be coordinated?

[The information follows:]

First off, Mr. Chairman, it is my experience as a nonepidemiologist, that the field of epidemiology is still in its infancy. It has accomplished small miracles in the field of acute and infectious disease and yet is only just beginning to develop the tools to provide major contributions to the study of the major chronic diseases.

In addition, Mr. Chairman, I should like to point out that like all scientific disciplines, the field of epidemiology provides us with some tools which permit us to seek the answers to major research questions. Thus the primary difference between our epidemiology group and those in other organizations will be in the nature of the problems they will be investigating. As to coordination, it is clear that the epidemiologists because of the smallness of their numbers, are able to keep in very close touch with each other whether they are in government or universities. In addition, I view it as one of my major responsibilities to insure the coordination of the research programs in my Institute with related programs elsewhere.

PERMANENT FACILITY

Mr. FLOOD. This time I want to begin at the beginning.

What is the status of that building we gave you the funds for in the 1976 appropriation? Have you let contracts?

Dr. RALL. The money has very recently been apportioned for it. We would expect that we would be able to award the contract sometime this summer.

Mr. FLOOD. I know this 1977 budget doesn't request any funds at all for the remaining construction phase of the building. What are you going to get, a partial building as of this morning?

Dr. RALL. I think I will defer to my colleague.

Dr. FREDRICKSON. It would be our intention, Mr. Chairman, to submit a request for the balance of the funds in the 1978 budget.

Mr. FLOOD. How about that, Mr. Miller?

Mr. MILLER. That is my understanding. I don't recall the request in 1977.

Mr. FLOOD. Mr. Natcher.

Mr. NATCHER. No questions.

Mr. FLOOD. Mr. Early.

Mr. EARLY. No questions.

Mr. FLOOD. Mr. Obey.

REDUCTION IN POSITIONS

Mr. OBEY. Some of these questions may be duplicative. Let me ask you, Dr. Rall: I see this year the administration has made significant changes in the attitude toward NIEHS, and has provided more funds than usual. At the same time they are asking you to cut back your intramural program by 33 positions. What research efforts will be reduced by this and what will the impact of that be?

Dr. RALL. That would prevent us from developing our epidemiology program, our behavioral toxicology program, and putting any additional effort on mutagenesis, but I gather from Mr. Miller that as of Friday there is hope those positions will be restored.

COST OF PERMANENT FACILITY

Mr. OBEY. Let me ask you about the cost of the building. What is the total cost of the building now according to your estimates?

Dr. RALL. The total cost will be $25 million already appropriated plus $42.9 million which is the current estimate of what it will take to build the remaining part of the facility. The total cost then is $67.9 million.

Mr. OBEY. By the way you were using the figure of $64 million last year, why the change?

Dr. RALL. This is the engineer's best estimate of the inflationary factors involved in delaying the letting of the contracts for the second phase.

Mr. OBEY. Why the difference between the 67 estimate and the 64 estimate last year? They must have taken into account inflation?

Dr. RALL. It is a year later. We can't let the contracts for the second phase until we have the money, and so we will only be able to contract for the first part, and the estimate is predicated on that.

Mr. OBEY. If this committee succeeds in what we tried to do last year to put the whole amount in, are we going to be faced with any addition above that estimate in the future, or can we be confident that it, in fact, is going to be the whole ballgame?

Dr. RALL. I am told that, if this amount of money would be available by the end of the calendar year, no additional funds would be required over and above the $67.9 million. Our engineer saw that, during this period of time really in calendar 1976, the building industry in North Carolina was in enough of a recession that they felt building costs would remain stable for calendar 1976. They are concerned that by the time we get into calendar 1977 they will increase at perhaps something in the order of 10 percent a year. That is why we are now concerned that, if we are not able to fund the second portion until next calendar year, the cost of that may increase 5 or 10 percent. These are all estimates, but they are the best our engineers can do.

Mr. OBEY. The President's budget provides no request for additional funds for the building?

Dr. FREDRICKSON. Not in 1977, Mr. Obey.

Mr. OBEY. In spite of our action there is no feeling it ought to be changed?

Mr. MILLER. In the fiscal 1977 appropriation, no; I don't think so. It will be reconsidered in 1978.

PERMANENT FACILITY—SPACE AND POSITIONS

Mr. OBEY. Last year Senator Biden challenged the need for this building, as you will recall, saying that it was just a space underutilized. How many square feet do you have in your current facilities per person?

Dr. RALL. Something in the order of 210, 220 square feet.

Mr. OBEY. How many would you have with the addition of 33 positions in fiscal year 1976?

Dr. RALL. That would bring it down to about 200.

Mr. OBEY. Dr. Major from the Center for Disease Control told my office that the ratio of scientific and technical personnel in space ranges from 300 to 700 square feet, depending upon whether you have relatively little equipment or a lot of large sophisticated equipment. Where would you rank your labs in that regard?

Dr. RALL. We have a lot of equipment. NIH has had a tradition of being able to do very good research for limited periods of time under very crowded conditions.

I would envisage that over the next few years our laboratories will become very crowded, indeed, and I think the scientists up to a point will be very productive if they can see clearly in the future that they will get relief from crowding.

Mr. OBEY. So by CDC's standards you are already crowded?

Dr. RALL. Yes.

Mr. OBEY. When that building is built, you will have room for how many people?

Dr. RALL. Approximately an additional 730 people, plus an additional 100 support facilities people such as shop maintenance, powerplant, and grounds maintenance.

Mr. OBEY. For a total of——

Dr. RALL. About 1,000, as we plan to retain our current facilities through 1990.

FORWARD PLAN

Mr. OBEY. How many people do you have on board under your forward plan by 1980?

Dr. RALL. Our forward plan does not really deal with numbers, positions. It deals with broad areas and dollars. The various projections of how our Institute should grow, which were begun in the late 1960's, would have showed that we would have, for instance, had the building by last year, I think, and would have had around 950 people employed at that time.

Mr. OBEY. 950 employed by when?

Dr. RALL. Last year.

Mr. OBEY. What is it reasonable to assume you would have employed under that plan by 1980?

Dr. RALL. Assuming that we do get full funding and the building is constructed, I would hope we could grow sort of incrementally each year to adequately assimulate the new people.

Mr. OBEY. I am trying to make sure the record reflects your staff positions in relationship to the need for the new building. You have a staff level at 300, and then all of a sudden you wave a magic wand and two-thirds of the building is sitting empty.

My question is if you are going to have a logical, orderly growth, it would seem that you ought to be putting more people on if you had any place to put them.

Dr. RALL. Yes, we have thought about this very carefully.

Mr. OBEY. Do you have any other facilities where you could put staff people for the next few years?

Dr. RALL. We probably cannot rent laboratory space but we can rent rather inexpensively office space, and our plans include moving all the people out of the offices that don't have to be right within the facility, to office space perhaps a mile away. That will allow us to bring scientists in who can at least use the office space and work in the laboratories, and allow for an orderly transition so that when the building is ready it will not be two-thirds empty.

Would you like me to submit a plan?

Mr. OBEY. Yes.

[The information follows:]

PLANNED GROWTH OF THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, 1976-83

	Permanent staff	Temporary staff [1]
Sept. 30, 1976	271	180
Sept. 30, 1977	331	180
Sept. 30, 1978	430	180
Sept. 30, 1979	510	180
Sept. 30, 1980 [2] [4]	[3] 700	180
Sept. 30, 1981 [4]	800	180
Sept. 30, 1982	900	180
Sept. 30, 1983	1,000	180

[1] Includes visiting scientists, guest workers, and temporary employees.
[2] Permanent facility opened during 1980.
[3] Approximately 90 positions are associated with operation of the permanent facility, such as the boiler plants, shops, and warehouse.
[4] During 1980 and 1981, the Institute will be relocating some of its research programs from its current facilities which will permit remaining programs to be expanded.

POSITIONS ABOVE 1976 LEVEL

Mr. OBEY. I would like to have your estimate of whether your positions above the FY 1976 level should be added to FY 1977 if you were to attain a reasonably orderly growth.

[The information follows:]

To attain a reasonably orderly growth, NIEHS would require an additional 50 positions over the 1976 level. Also, 10 additional positions would be required to design, manage, and monitor the Mutagenicity Screening Program.

PLANNED GROWTH

Mr. OBEY. Could you supply for the record a chart showing also what the planned growth for the Institute was when it was created in terms of positions and funding from the day it was created to the present?

I would like it in chart form.

Dr. RALL. Yes.

Mr. OBEY. If you could allow for inflation so that we can see what the funding level would be if the original commitment to the Institute had been kept.

[The information follows:]

Planned Growth of the Institute

At the time early planning of the National Institute of Environmental Health Sciences was undertaken, it was proposed that the Institute would be limited to intramural research and contract supported research. It was not until 1966 that the decision was made to transfer the program from the Bureau of State Services to the National Institutes of Health and include an extramural program as part of the Institute.

In its planning to develop the more limited National Environmental Health Sciences Center (now the intramural program of the NIEHS) the Bureau of State Services called upon the Research Triangle Institute to develop recommendations for the development and operation of the Center. What follows is extracted from that report and was submitted to the Government on October 31, 1965.

Foreword

This report, "Recommendations for the Development and Operation of the National Environmental Health Sciences Center," is submitted to the Bureau of State Services (EH) of the United States Public Health Service in fulfillment of Contract No. PH 86-65-109 dated June 14, 1965, and contains recommendations pertaining to major componets of the NEHSC program, scientific staff, supporting technical activities, general technical facilities, the schedule for development of the Center's program, and relationships between the Center and academic institutions. The Research Triangle Institute's study has been directed toward the scientific aspects of the Center and its program. This report does not consider details of space and staff for such administrative functions as personnel, accounting, purchasing, and maintenance, nor the space requirements for such facilities as cafeteria, warehousing, and supply stores, although they obviously are necessary elements. The report is in two sections: the main body contains the recommendations and necessary supporting detail, and the appendixes provide design data and pertinent supplementary information. Because of the importance of Center-university relationships in carrying out the NEHSC program, a special addendum, "Relationship of the National Environmental Health Sciences Center to the University Community," will be submitted, incorporating recommendations for establishing a viable relationship between the staff of the Center and those of the academic community.

The recommendations contained in this report are to be considered as guidelines for the development and operation of the National Environmental Health Sciences Center. Laboratory design and experimental techniques are advancing; and as decision points are reached in the design of the facility and the development of the Center's program, the best current advice should be sought.

Summary

Man's health and well-being are intimately linked with his environment. The complexity of this environment and the manner in which it might influence man's health have been greatly enlarged by an increasing population and an advancing technology. Some of the environmental problems, in areas such as water and atmospheric pollution, have been recognized for many years and the U.S. Public Health Service through its categorical programs is responsible for devising remedial measures.

But the experience gained through the categorical programs has brought other factors into relief; for instance, the dependence of the body's response to one stress on the simultaneous presence of other stresses; the basic nature of the body's reaction to different stresses and different levels of the various stresses; the difficulty of properly assessing the significance of a recognized environmental hazard without adequate knowledge of others which may act concomitantly. Because of limited knowledge of such matters and the necessity for the categorical programs to respond quickly to specific situations, the remedial measures have had to be designed without knowledge of interrelations, or indeed of the nature and levels of unrecognized hazards which may be of considerable importance to longevity and to full retention of human function and ability.

In a society where good health and well-being of the individual and the realization of each man's full potential are among the central objectives of the nation, it is essential that there be continuous long-term and intensive study of environmental factors which may be inimical to these ends. The effort required is of great magnitude for the problems are quite complex and difficult of identification,

and the knowledge necessary for an effective solution will often have to be generated in new laboratory and field studies.

The knowledge essential for a more effective environmental health program can be obtained, for the sophisticated tools of science even now available are such that considerably better and more penetrating insights can be achieved than was possible before this decade. If, on a sufficient scale, these tools are applied to determining the relations of health and environment, it is certain that new and often unexpected causative and interrelated factors will be discovered. Such discoveries will furnish the basis for establishment of more effective remedial measures.

Because of the complexity and ramifications of the problems, the best use of present knowledge and the generation of new germane knowledge can be accomplished most efficiently by highly competent personnel working in well-planned specialized facilities, with first rate research equipment and research assistance at their disposal. Such a combination can be counted on to contribute major new advances in the field of environmental health; these advances will include increased abilities to recognize hazardous environmental factors, a better understanding of how these factors affect the health of man, and a scientific basis for devising effective remedial measures. The alternative of such investigations appear to be the continued development of environmental conditions which may increasingly become alien to the objective of good health and well-being of man.

The central problem of the relation of environment and health has been recognized by the Congress, and the establishment of a National Environmental Health Sciences Center has been approved. In the several documents leading to the approval it was implied that the Center would be the best means of directly and indirectly focusing in concern, the investigative talents of highly qualified scientists of many disciplines on the general and specific problems of the environment and its relation to health. The present study, undertaken by the Research Triangle Institute under a contract with the Bureau of State Services (EH) of the U.S. Public Health Service, finds this implication to be fully justified.

The Research Triangle Institute, by making use of various documents, its own competence and a number of highly qualified consultants in pertinent disciplines, has critically examined the various areas considered essential to the fulfillment of the task of the Center. In light of this examination a number of general observations and recommendations are made.

The mission of the Center, taking cognizance of the thoughtful attention given to this matter by many individuals and groups, appears to be expressed best by the following statement:

"The National Environmental Health Sciences Center will provide for the determination, study, and evaluation of the effects of environmental factors, singly and in the aggregate, upon the health of man. Its program will be directed to a better understanding of the complex, interrelated phenomena underlying the human body's reaction to the increasingly wide range of chemical, physical, biological, and social environmental influences imposed by modern living, with the objective of developing the knowledge necessary for devising effective measures to protect man from environmental factors found to be harmful."

Thus, the National Environmental Health Sciences Center will take its place alongside the categorical programs of the Public Health Service to fulfill a vital national need for determining and evaluating the effect of the totality of environmental factors on the health of man and of investigating means to protect against those factors found to be harmful.

The broad research programs of the Center may be defined by the following areas:

Investigations of the changing spectrum of disease which results from changes in the technosociological environment in order to aid in anticipating future health problems,

Investigations to determine the causative and aggravative factors associated with observed deleterious health effects,

Studies to identify those areas of research which are being neglected in the broad-front attack on environmental health problems, and

The development of new knowledge necessary to attack environmental health problems.

These broad program responsibilities will require a wide range of competent individuals working together in a well-integrated multidisciplinary effort. This can be achieved by forming a number of components of centers of interest, each multidisciplinary in composition though titled by a discipline descriptive of that component's chief responsibilities. It is recommended that the components be:

Epidemiology, toxicology, physiology, pathology and cytobiology, analytical methods, bioengineering, biometrics and computer services, animal production, and technical information services.

It is believed that a rigidly predetermined organizational structure which artificially groups any of these components or subverts any one to another would be inimical to the development of the most effective multidisciplinary research effort.

It is therefore recommended that:

The directorate of the Center be given the flexibility to develop an organizational structure which continually encourages a multidisciplinary focus on environmental health problems and the details of organization be governed by the requirements of the research program.

The need for the effective and prompt utilization of the Center's resources in a research program of this broad nature places a much greater responsibility on top management than that normal to most organizations. In order to provide the information and judgment necessary for decision and action, it is recommended that the Director have the following groups assist him:

A program planning staff within the center whose responsibility would be to critically review the internal and external research programs of the Center in light of national activity in the environmental health field, to assure that the Center's activities are consistent with and contribute to fulfillment of the mission of the Center.

A policy advisory group of external scientists particularly knowledgeable in the fields of public policy, management, industrial hygiene, engineering, and environmental medicine who would advise on the significance of problems that are identified in various environmental situations and who would be alert to potential sources of environmental problems.

A scientific advisory group of external scientists whose association with basic scientific fields would provide the Center with input on the most advanced work in the basic disciplines of importance to pursuit of environmental health problems.

The need for excellence is a theme which has been emphasized in previous studies and has been emphasized strongly throughout discussions leading to the development of this report. The ultimate success of the Center will depend primarily upon the individuals selected as director and as leaders of the component scientific groups, and upon the capacity of the Center to recruit a competent scientific staff appropriate to the needs of the developing research program. To this end, it is recommended that:

The principle of vertical staffing be followed (that is, filling of positions from the top downward) but with the flexibility to allow acquisition of high quality staff in the absence of a completed scientific management staff,

Proportionately equal growths in each of the technical components be emphasized in order to maximize the probability of intercomponent effort and communication,

There be recognition in personnel allotments that the advanced research character of the Center will require a scientific staff whose average civil service rating will be higher than normally found in many government installations,

There be recognition of the need for remuneration beyond the maximum salary levels now set by law for a small number of top scientists and physicians,

The allocations for personnel and for program funds recognize the need for Center management to have confidence in active top-level support for the ultimate size and caliber of the scientific program and for resources to acquire staff to achieve, on an orderly schedule, a personnel level of 1,000 by the early 1970's,

Provision be made to encourage development of exceptionally strong university-Center relationships. (This is considered to be of such importance that an addendum report is being prepared.)

In order to promote the exchange of information and increase the probability of new ideas, the Center should aggressively seek to attract outside scientists to the Center for periods of a few months or more, professors for summer terms or during their sabbatical leaves, and graduate students for graduate research programs. In order to promote the exchange of knowledge and to encourage interest in the basic problems of environmental health, it is recommended that:

Provision be made in facilities and funds to attract outside scientists to the Center for periods of a few months or more.

The total climate of the Center should encourage these relationships. The attitude of the scientific directorate and the individual scientists of the Center, as well as the attractiveness and adequacy of the physical facilities, will be of primary importance in achieving this objective.

The physical facilities of the Center must be designed to encourage the maximum scientific response and effectiveness from the research personnel and to anticipate the possibility of research plans which lie beyond those presently foreseeable. Thus, it is recommended that:

A master plan be developed which will give careful consideration to long term projections and will best accommodate to the mission of the Center, its personnel and the relation of the Center to its present or likely future neighbors,

Careful consideration be given to the facilities of the several basic components which require proximal locations because of related and interrelated functions,

Considerable flexibility be incorporated in nonspecialized laboratory space to allow for future equipment and for the best accommodation to a developing program,

The animal facility be programed for completion at least 2 years prior to the date for occupancy of the main facilities as such a lead time is necessary to assure a reasonably well characterized animal colony,

The facilities requirements detailed in the report appendix serve as the general guide for architectural and engineering planning. (These requirements have been studied critically by leading investigators in the appropriate fields and, in light of the Center's mission, are considered necessary and adequate.)

In order to carry out its mission, the Center must have not only a highly competent scientific staff working in efficient and specialized facilities, but it must have an adequate complement of good equipment. In view of its vital mission the Center may well need to be the best equipped life sciences laboratory in the world.

The concern for the adverse effects of environmental factors on man's health, which prompted Congress in 1960 to ask the Surgeon General to make a thorough study of environmental health problems, has not lessened in the intervening years. Indeed many problems are now recognized which need exploration and can be initiated with assurance that they will be fitting components of the research program of the Center.

Some examples of such basic areas of research are: Studies of the reactions of living organisms to environmental stresses, elucidation of the mechanisms of toxic response, studies of the chronic effects associated with the duration and repetition of exposure, studies of the effects of environmental stresses in the aging process, and studies to develop the criteria for determining the state of health in the absence of clinical symptoms. Since investigation in many of these areas require animal experiments, the need for early and rapid development of suitable animal colonies is emphasized. Recognizing that the Center's research program should begin as soon as possible, rather than awaiting completition of permanent facilities, the Public Health Service has made provisions for leasing interim facilities.

The Center must participate in and initiate, where needed, the development of the communication channels which will integrate into a national program: Its own research, the basic research of the National Institutes of Health and the university community, the applied research of the categorical divisions of the Public Health Service, and the practical knowledge of industry. This integrative effort will necessitate the full use of the working channels between the Center and other components of the Public Health Service; the establishment of a means for obtaining pertinent industrial data; and the development of new and imaginative patterns of university-Government relations which will most effectively make use of the resources of the academic community with mutual benefit to both the Government and the academic institutions of the Nation.

The recommendations contained in this report are made with the objectives of establishing the National Environmental Health Sciences Center as the focal center for a comprehensive attack on the environmental health problems of the Nation.

INTRODUCTION

Man has been aware for many decades that the environment in which he lives, his contamination of it and the degree to which he can control that contamination, determine in some measure his state of health. Through technological and social changes man has added new factors to an originally virgin environment and too often has found these factors to be antagonistic to his health. Some of these factors have been readily identified and the Public Health Service, through its categorical programs in air pollution, water pollution, occupational health, radiological health, environmental engineering and food protection, has assumed

responsibility for devising control procedures for them. Because their effects have been more subtle, additional environmental factors are only now beginning to be recognized. As our knowledge of their effects increases, so does our apprehension about their influence on man's health, particularly as man modifies them for good or bad. Many individuals, groups, and committees have considered the evidence and have concurred that a focal point or cented is needed to carry the responsibility for an overall purview of the effects of the totality of environmental factors, natural and man-derived, upon the health of man.

Early in 1960 the House Appropriations Committee, aware of the increasing evidence of man's creation of a potentially hostile environment, requested the Surgeon General to "make a thorough study of the environmental health problems and the most efficient organization of our facilities to meet these needs * * *". As a result of recommendations of a study group assembled to carry out this request, the Surgeon General submitted a proposal in June, 1960, for a consolidated environmental health center which would provide "a central campus facility for research, overall program administration and coordination * * *, supplemented by regional field facilities". The then proposed 2,500 man facility had as its primary objective the "unification of all the Public Health Service's environmental health programs and greatly expanded facilities".

In considering this proposal, the President's Science Advisory Committee Ad Hoc Panel on Environmental Health (May 18, 1961), agreed that "there is an urgent need for expanded activities in research and control measures related to environment health * * *" but "did not feel that enough effort had been directed to identification of major problems and drafting of the blueprints of specific research to be undertaken."

As a result of these recommendations, the Surgeon General established the Committee on Environmental Health Problems (Gross committee) in August, 1961, to develop long-range objectives for the environmental health program of the Public Health Service. In its report (published in 1962), this committee further advanced the concept of the need for a strong focal center for control of environmental hazards and, in addition, recommended the establishment of a new Office of Environmental Health Sciences. Independent of the divisional structure, consisting of scientific groups "which would be specifically charged with the continuing responsibility for an overall purview of the entire field of environmental health, (and) would include biological, physical, and social scientists as well as mathematicians, free to study basic problems in environmental health and undertake research on problems of common interest to the several operating units where desirable, while providing advice and consultation to the Bureau of Environmental Health, with respect to the overall direction of research."

'As a result of proposals by the Surgeon General during the budget hearings in 1963, Congress appropriated funds for new programs in environmental health sciences for fiscal year 1964 (FY 64). In his fiscal year 1965 budget message to Congress, the President proposed a national research facility in environmental vironmental health and Congress appropriated funds for planning this facility.

Following the recommendations of a site selection commitee, which considered a number of possibilities in the light of specified desiderata, the Secretary of Health, Education, and Welfare announced on January 7, 1965, that the Center would be located in the research triangle area of North Carolina. This area is located centrally with respect to Duke University in Durham, the University of North Carolina in Chapel Hill, and North Carolina State University in Raleigh. The area includes the laboratories of the Research Triangle Institute, founded at the end of 1958, through the combined efforts of the three large universities, the business and industrial community, and the State of North Carolina.

With the gradual transition away from the 1960 concept of a large consolidated environmental health center responsible for overall administration and coordination of expanded activities of a divisional nature, another concept, initiated by the Gross committee, became progressively clearer—that of the need for a comprehensive program of research in environmental health sciences to provide a better understanding of man's interaction with his environment. The necessity for redefining the center concept was reinforced by decisions to reduce its contemplated size to 1,000 to 1,200 persons and to locate it away from the Washington area. The Public Health Service developed this concept in a preliminary program document and, with its consultants, prepared tentative organization and staffing plans, facility requirements, and a schedule for establishing the Center.

At the suggestion of the Office of Science and Technology, the Surgeon General submitted these staff papers to a subcommittee drawn from the National Environmental Health Advisory Committee and headed by Dr. Detlev W. Bronk, to consider the mechanisms by which such an undertaking might best be implemented. The Bronk committee recommended that the Center be operated by the Public Health Service rather than through contracts with a university or university group.

It also reemphasized the need by expressing its belief "that the proposed Center will fill a vital national need with the purpose of studying and determining the effect of environmental factors, singly and in the aggregate, upon the health of man and the protection of man's health against harmful environmental agents." In commenting on the Research Triangle Park in North Carolina as the site for the Center, the committee pointed out the value of university relationships and expressed the belief that the Center, favorably located with respect to the three strong universities "could develop a new and imaginative pattern of university-Government relations in the conduct of Federal laboratories. . . ." Following the recommendation of the Bronk committee, the Research Triangle Institute was asked to study the concept, PHS plans, and other related material, and make detailed recommendations for the development and operation of the National Environmental Health Sciences Center. The Institute's assignment included review of, and recommendations pertaining to, major components of the Center's program, required staff, supporting technical activities and services, general facilities and equipment requirements, the schedule for development of the Center's program, relationships between the Center and academic institutions, and utilization of scientific and technical resources of the region.

While carrying out this assignment the Research Triangle Institute secured the assistance of a number of scientists recognized for their accomplishments in studies of environmental health interest.[1] Many of these scientists met with the RTI staff as a study panel on July 12, 13, and 14; undertook individual assignments relating to elements of the Center's program; and met again, as a group, on August 25 and 26. The scientists who participated in the RTI study panel meetings, and who represent a broad segment of the scientific community, unanimously requested that their strong endorsement of the Public Health Service concept of the Center, as reviewed by the Bronk committee, be recorded.

In addition to containing specific recommendations resulting from the assigned study, this report attempts to synthesize the considerations of numerous individuals, committees, and subcommittees (both within as well as external to the Public Health Service) which have concerned themselves with the definition, development, and operation of an effective program.[2]

Mission

Cognizant of the thoughtful attention that many people have given to the need for a National Environmental Health Sciences Center, we believe the mission to be expressed best by the following statement:

The National Environmental Health Sciences Center will provide for the determination, study, and evaluation of the effects of environmental factors, singly and in the aggregate, upon the health of man. Its program will be directed to a better understanding of the complex, interrelated phenomena underlying the human body's reaction to the increasingly wide range of chemical, physical, biological and social environmental influences imposed by modern living with the objective of developing the knowledge necessary for devising effective measures to protect man from environmental factors found to be harmful.

In its consideration of the long range objectives of the environmental health program of the Public Health Service, the Gross committee observed that "Projections and predictions abound which purport to describe the growth of the American population in the remainder of this century, and the increasing fraction of older individuals in the population; the ever-increasing complexity of our technology; the development of new industries, and increasing reliance on nuclear power; the magnitude of the gross national product; the magnitude of the national agricultural effort; the introduction of new chemicals into our food, water, air, clothing, tools, and toys; the coalescence of huge metropolitan areas;

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[1] See app. I for list of participants in this study.
[2] See app. II for bibliographic material considered during this study.

altered means of communication and transportation; new modes of dress; increased leisure time and the demand for recreational facilities. The exact magnitude of any one of these projections may be open to question, but their trend is all too apparent. And from these technological, agricultural, economic and social changes must, inevitably, arise a panoply of diverse problems in environmental health which must be solved before they are permitted to become acute."

The categorical divisions of the Bureau of State Services (Environmental Health) have been charged with specific investigative, control, and regulatory responsibilities in the fields of air pollution, water pollution, radiological health, occupational health, environmental engineering, food protection, public water supplies, and recently, with similar activities related to pesticides and solid waste disposal. These categorical activities have already gone a long way toward defining the more outstanding pollutants and hazards and toward devising methods for control. But as this knowledge increases, hazards associated with the interaction of newly recognized factors come into relief: The importance of basic body reactions to the various stresses, the effect of social pressures, the dependence of response to one hazard on the presence of others, and the difficulty of assessing the significance of one circumstance or condition without an adequate knowledge of others. In the conduct of their responsibilities, the categorical divisions must necessarily be concerned with current significance and applicability. The breadth of this activity precludes the investigation in depth of the longer-term effects brought on by the complex interaction of environmental factors which transcend the boundaries of the categorical units.

A study of the activities of the National Institutes of Health, the industrial hygiene and occupational health departments in industry, and the university research programs shows that while many resources are now devoted to various aspects of the influence of the environment on man, there is yet no group of scientists charged with cognizance of the impact of the whole environment on man. This shall be the responsibility of the Center.

It is a vast charge. It will require the collection of environmental health information from many resources for the purpose of integrating it into a meaningful whole from which pertinent deductions can be made regarding the occurrence of present and future health problems and their mitigation. Thus, the National Environmental Health Sciences Center will take its place alongside the categorical divisions of the Bureau of State Services and the National Institutes of Health fulfilling a vital national need for determining and evaluating the effect of the totality of environmental factors on the health of man and of investigating principles of protecting man's health against those found to be harmful.

The growing realization of the importance of environmental factors to the state of man's health has created university, private, and government support for extensive research efforts in various specific fields associated with environmental health sciences. In contrast, it is the mission of the National Environmental Health Sciences Center to achieve that overview necessary to insure that the total field of environmental health is covered, and to give particular attention to those effects which may be insidious. The Center's activities may be characterized as:

Identifying present and potential health problems associated with environmental factors through studies of disease and disability patterns;

Identifying gaps in our knowledge which impede the solution of these problems; and

Providing for the development of this knowledge through extensive programs of grants and contracts and intensive programs of inhouse research.

The identification of deleterious health effects and their probable causes is obtained through observations of the results of natural experiments in man's environment where many environmental factors are at work. Tentative associations resulting from these observations provide hypotheses which can be tested in the controlled experiments of a laboratory or in analytic epidemiological studies in the field. The laboratory and field efforts work in concert to provide a more positive identification of a particular cause-effect relationship.

While dramatic advances in computer technology in recent years provide the means to handle the large quantities of statistical data necessary for such studies, study results are often impaired by the inability to make meaningful measurements of all the variables involved. In order to relate disease patterns to environmental influences, we must not only measure the state of health of a population, we must also be able to quantify the associated environmental factors.

At present, the state of health of a population is obtained from vital statistics and Public Health Service morbidity data; but these data are gross. Methods

must be developed for describing states of health short of death or diagnosed disease, in order to detect health problem trends before the problems become acute. This will require extensive investigations into the physiological deviations from "normal" health and these investigations, in turn, must be buttressed by a marked improvement in the analytical methods used to measure the deviations.

Improvements are necessary in our ability to measure and categorize environmental factors such as humidity, odors, noise, heat and vibration; chemical pollutants and viral bacteriological contaminants in air; water and food; urbanization; automation; and others. This will require better analytical techniques as well as the development of suitable field methods and equipment. Categorization of environmental factors on the basis of their effect upon the human organism would be valuable, but this is hampered by our meager knowledge of the basic body reactions to environmental stresses.

Finally, these studies must be supplemented by research into the adaptive mechanisms of man and the fate of environmental agents, in order that the deleterious effects of undesirable environmental influences may be mitigated.

This discussion serves to point up the broad-scale research effort that must be undertaken to understand the antagonistic environmental influences man inflicts upon himself and, in turn, to protect him from them. This research activity can be defined by the following program areas:

1. Investigations of the changing spectrum of disease which results from changes in the techno-sociological environment in order to aid in anticipating future health problems;
2. Investigations to determine the causative and aggravative factors associated with observed deleterious health effects;
3. Studies to identify those areas of research which are being neglected in the broad-front attack on environmental health problems; and
4. The development of new knowledge necessary to attack environmental health problems.

This is indeed a broad research effort. It deals with man and his living conditions; the ways in which these conditions interact with one another and with man to affect his health and well-being; and with the discovery of principles whereby man may learn to control those interactions found to be harmful. The four program areas are discussed in some detail below.

1. Investigations of the changing spectrum of disease which results from changes in the techno-sociological environment, in order to aid in anticipating future health problems

The objective of such investigations is the identification of patterns of health problems associated with major technological or sociological innovations in order to form a basis for predictions that could lead to preventive measures. The epidemics of typhus, typhoid, and tuberculosis which followed the industrial revolution were brought about by the inability of the cities to cope with the unhygienic conditions that resulted from the rapid influx of new populations. As sanitary conditions were improved these diseases decreased, but at the turn of the century new diseases became more prevalent, particularly respiratory and gastro-intestinal disease of infants. With further improvement of the sanitary environment these diseases also declined in importance, but outbreaks of paralytic poliomyelitis began to occur with distressing frequency. Following World War I the "older" diseases declined rapidly but "newer" epidemics were becoming important health problems, among them the emergence of duodenal ulcer as an important cause of morbidity. In turn, these declined and have been replaced by hypertension, leukemia, coronary heart disease, chronic bronchitis and emphysema, and the most dramatic, lung cancer. These now form some of our modern "epidemics".

The processes responsible for these changes, the decline of some diseases and the emergence of others, are imperfectly understood. Some factors, including changes in diet; housing, working conditions and physical activity, increase of atmospheric pollutants, cigarette smoking, and emotional strain have been implicated with varying degrees of assurance. Nevertheless, a shadowy picture does emerge which indicates that at any point in time the diseases which most afflict a population are a reflection of the existing social and technological climate of that time. The older diseases were consequences of a web of factors which included poverty, crowding, long working hours and poor housing. The newer diseases appear to be associated with some of the concomitants of affluence—sedentary living, high-fat diets, increased atmospheric pollution, the

pressures of modern living, etc. The increase in mental disorders is believed by many to be a consequence of the increasingly complex social and technological environment in which we live.

A multidisciplinary group capable of integrating, synthesizing and interpreting vast amounts of data that could be drawn from different fields and of varying levels of complexity and organization could deduce valuable information from these patterns to aid in delineating future trends in health effects.

2. Investigations to determine the causative and aggravative factors associated with observed deleterious health effects

The objective of such investigations is the identification of environmental factors causally related to disease conditions, in order that efforts may be undertaken to eliminate or moderate their effect. The ability to handle vast amounts of data, to correlate and analyze it, is made possible only by the availability of modern electronic computers. For example, it has been observed that there are higher incidence rates of leukemia, kidney stones, stomach cancer and diphtheria in certain geographic areas. It is not yet known to what extent these are associated with particular environmental factors.

It is important to determine the extent to which environmental influences are causative or aggravating, and the extent to which multiagent effects are important. Physical stresses such as heat, noise, vibration, and non-ionizing radiation should be evaluated in relation to disease states.

Studies of broad health-environmental relationships such as the effect on health of heavy industry, and the effect on health in the developed countries of modern life including such things as decreased physical activity and increased food consumption. We need to know more about the effect of prepared foods or the effect of rapid transportation on body systems. Studies should be made of the comparative health of persons exposed to special environments (e.g., certain industrial climates, climate extremes) and of the comparative health of persons exposed to special potential agents (e.g., chemicals, radiation, certain foods) and the extent to which these agents may aggravate other health defects.

Biometeorology becomes an important subject in epidemiological studies because many environmental agents in air and water are transported over considerable distances and are subject to modification by environmental factors. It is well known that meteorological conditions can bring about concentration or dispersion of agents and modify man's reactions to many kinds of stresses, as well as effecting him directly.

The stresses associated with modern social pressures are beginning to be recognized as important environmental influences. There is much testimony that urban crowding, financial insecurity due to automation, and the clashing changes in the cultural patterns of families and groups are imposing mental stresses which are contributing to behavioral disorders. Thus, the sociologist and psychologist, as well as the life scientist and meteorologist, must be called on to participate in epidemiological studies.

3. Studies to identify those areas of research which are being neglected in the broad-front attack on environmental health problems.

The objective of this program is to provide that overview of environmental health sciences activity which will point up areas of research that must be pursued in order to provide man with the knowledge to promote a healthy environment.

The Center, through its close working relations with all other activities in environmental health science, must be well informed on progress being made elsewhere on the effect of environment on man's health. The Center must become the chief resource for information on environmental health matters. It can then direct its own research most effectively, and can better encourage others through grants, contracts, training aids, and other means, to contribute to the basic and applied knowledge which bears on solutions to problems in environmental health.

The better understanding of the broad spectrum of environmental health activities will arise from a variety of sources, including the National Institutes of Health and the categorical programs of the Public Health Service, the university departments of preventive medicine and schools of public health, industrial hygiene and occupational health departments, and the applied and basic investigations in life sciences carried out in university, industrial, and private laboratories. The range and fertility of these sources will require that the Center have an extensive capability in information storage and retrieval as well as an intimate familiarity with other information centers, both Government and non-Govern-

ment. The knowledge available even now, coupled with the increase emphasis on creating new environmental health knowledge requires that the Center take an active role in the nation's programs for developing effective information storage and retrieval techniques.

4. The development of new knowledge necessary to attack environmental health problems.

The objective of this program is to provide for the development of the knowledge necessary (1) to identify and measure environmental agents, (2) to measure the state of health of the host, and (3) to measure the apparent, unknown, or latent response of the host.

This knowledge is fundamental to the pursuit of the Center's mission and, because of our lack of this knowledge, acquiring it will constitute a major portion of the Center's internal research effort. Indeed, because of our great lack of understanding, the Center must aggressively seek ways to encourage others to supplement its own efforts through programs of grants, contracts, training aids, and by all other means which may be available.

Little is known about man's response to the burden of environmental stresses of various kinds, levels, and complexity. We must understand the mechanisms of reaction of living organisms to these stresses in order to devise the means for combating them. Such understanding may provide a valuable contribution to means for categorizing environmental influences by their effect upon the living organism. This understanding results from a synthesis of epidemiological observation and of laboratory experiments which are designed to maximize the assurance with which experimental data can be extrapolated from animals to humans.

We need to be able to recognize early indications of toxic response, and to be able to identify individuals or populations which have abnormal susceptibility to specific toxic agents. We also need to be better informed about chronic effects due to duration of exposure and repetitive exposure. Valuable information for guiding research in these areas has been accumulated by the industrial hygiene and occupational health departments of industries which have maintained records of exposure of workers to various environmental influences.

One of the important gaps in our knowledge of health and disease relates to criteria for measuring degrees of health. It has been necessary in the past to define health in a negative sense; that is, as the absence of disease. To assess the significance of chronic exposure to environmental factors and the significance of the burden due to multiple stresses, means must be developed for measuring deviations from positive state of health. This, in turn, leads to the need for defining health, not as the lack of disease, but in a positive sense which recognizes man's potential to achieve a full state of health, perhaps even beyond that which he now deems desirable.

This definition of health would be expected to depend upon sex, genetic factors, previous health history and, most of all, age. The young and the old have little immunity or resistance to disease, but the effect of stresses upon the aging process itself is not yet known, nor do we know what effect aging has upon the individual's response to environmental stresses. The impairments resulting from exposure to stress are difficult to distinguish from those associated with the normal aging process. Therefore, normal patterns of aging must be defined, and a considerable effort towards understanding the aging process is already underway in NIH laboratories and at universities. However, because of the importance of the aging process in environmental health studies, the Center should undertake research activity of interest in its mission in order to fill our knowledge gaps in an orderly fashion.

The research to develop new knowledge depends upon experimental studies with animals and cell culture populations, as well as organ culture and other invitro systems. Thus, the development of experimental subject colonies is vital. The characterization and maintenance of such experimental populations is a major task, and it is an essential task for the success of experimental work at the Center. The validity of extrapolations from animal experimentation to meaningful postulates for man will require a depth of insight into animal subjects that has not yet been attained. In the important studies to define a positive state of health, we must learn to raise healthy animals. Furthermore, a cage living is not normal living, so studies must be undertaken to distinguish between the effects of stress arising from the caged conditions and the effects of stress imposed by experimental agents.

Inherent in all of this discussion is the need for meaningful measurements. While many advances have been made in analytical techniques and in the application of bioengineering methodology to experimental measurement and control, the projected program investigations will call for substantial improvements, not only in the sensitivity of present techniques, but also in the development of new techniques and methods to meet these advanced requirements.

The few program areas that have been outlined and the examples of problems that have been given are in no sense restrictive, but are representative of the broad nature and the magnitude of effort and resources needed over the next decade.

The Research Triangle Institute agrees with the gross committee that further detailing of programs and projects is complicated by "the important fact that the conditions encountered in the environment which affect health are changing rapidly and all too often unpredictably". The particular projects that are undertaken to pursue the Center's mission in the above program areas must be the responsibility of the director and his planning staff. It is recommended that, in the initial stages of program development, emphasis be placed upon a series of projects intended not so much to give answers to particular questions as to give early validation to research approaches to the many complex questions that have been raised.

In contributing in a major way to the national effort on environmental health, the Center will act as the focal point for a comprehensive attack on environmental health problems. This Center must participate in and, where needed, initiate the development of the communication channels which will assist in the integration into a national program, the applied research of the categorical divisions of the Public Health Service, the basic research of the National Institutes of Health and the university community and the practical knowledge of industry. This integrative effort will necessitate the full use of the working channels between the Center and other components of the Public Health Service, the establishment of a means for obtaining pertinent industrial data, and the development of new and imaginative patterns of university-Government relations which will most effectively make use of the resources of the academic community with mutual benefit to both the Government and the academic institutions of the Nation.

TABLE II

Projected Staffing

Components	FY 66	FY 67	FY 68	FY 69	FY 70	FY 71	Early '70's
Epidemiology	↑	↑	↑	↑	↑	↑	80
Toxicology	↑	↑	↑	↑	↑	↑	135
Physiology	↑	↑	↑	↑	↑	↑	85
Pathology and Cytobiology	↑	↑	↑	↑	↑	↑	80
Analytical Methods	↑	↑	↑	↑	↑	↑	130
Bioengineering	↑	↑	↑	↑	↑	↑	65
Biometrics and Computer Services	↓	↓	↓	↓	↓	↓	65
Animal Production	↓	↓	↓	↓	↓	↓	65
Technical Information Services	↓	↓	↓	↓	↓	↓	40
Training	↓	↓	↓	↓	↓	↓	15
Program Direction and Services[1]	↓	↓	↓	↓	↓	↓	240
Estimated Total	33*	165	330	500	650	800	1,000

[1] Assumes provision of basic custodial and guard services by contract.

*RTI is informed that 33 positions are provided in the current fiscal year (1966) for staffing NEHSC activities.

As mentioned above, the early planning for the Institute did not envision that it would engage in the support of research and training through grants. Thus, the first long range budget plan for the total Institute was not developed until December 13, 1966.

Relevant extracts of that plan follows:

PRELIMINARY 5-YEAR PLANNING DATA SHEET

DECEMBER 13, 1966.

Organization: Division of Environmental Health Sciences, NIH.
Appropriation: 7570362.

Problem

The mission of the Division in both its intramural component, the National Environmental Health Sciences Center, and extramural program of support, will be to provide a scientific base for those units of the U.S. Public Health Service charged with the responsibility for establishing standards and enforcing regulations in the general area of environmental health with particular emphasis to the needs of the Bureau of Disease Prevention and Environmental Control.

The increasing number of agents being introduced into the environment both intentionally and adventitiously requires an assessment of real and potential hazards by bioassay techniques and the elucidation of principles of biological action since testing of all environmental agents is manifestly impossible.

There are no sciences that have a peculiar or unique relevance to environmental health. Nonetheless there are groups of compounds which impinge upon biological systems in concentrations and for durations that are determined by environmental factors and with little relationship to the likes or dislikes of individuals or small or large population segments. Most of these have high inherent biological activity and impinge upon biological systems for very long periods of time, usually in low concentrations. These compounds are potential hazards to health; generally speaking they do not have demonstrated capability to produce disease under the circumstances usually encountered. The examples of acute intoxication by these substances do not constitute a frame of reference against which the effects of chronic exposure at low levels can be predicted. Consequently, there is no science base upon which to develop control measures to limit these hazards to health.

Goals and target dates

The encompassing goal is the development of a cohesive framework within which the various scientific disciplines and categorical needs concerned with environmental health can operate in a collaborative and interrelated manner to facilitate the achievement of maximum information for use in limiting deleterious effects of environmental hazards.

The center of the scientific interest will be the phenomena associated with the source, distribution, mode of entry, and effect of adventitious chemical and biological substances upon biological systems in relation to the health and well being of human beings. The area of inquiry will encompass the epidemiology of environmental hazards, the dynamics, reaction kinetics, and modes of transmission and entry of such substances; the short and long-term toxicological and morphological effects upon biological systems, both animal and man. The objectives of this inquiry will be to assess the actual and potential risks associated with exposure to adventitious environmental hazards; to determine tolerances and threshold of hazard to biological systems as a guide for control policies, and elucidate mechanisms and mode of action as a basis for the development of control technology.

Consideration in the development of program will be given to the determination of the need for study of existing or potential hazards. This can be accomplished by the utilization of clinical, epidemiological, and biometric data identifying individuals or groups with signs and symptoms of toxicity or population segments at unusual risk to environmental hazards. A second base for program is the review on a continuing basis of the chemical and physical structure and properties of existing and potential environmental agents for the purpose of identifying those of likely toxicologic significance, e.g., compounds chemically related to known economic poisons, etc. The identification and extent of the hazard can be pur-

sued along three lines: (a) the population involved, its size, characteristics, including geography, and occupation factors and subsegments, such as extremes of age and associated diseases: (b) the nature of the agent, including its chemical, biological and physical properties as indices of suspicion, and (c) the environmental location—air, food, and water.

It is unrealistic at present to identify target dates in advance of initiation of the environmental health research program. As implementation progresses in a well-planned sequence, each phase as it develops should at an early date provide a basis for estimation of target dates recognizing the latitude inherent in predicting the results of research endeavors.

The target dates for the achievement of goals require special consideration since of necessity they are now primarily oriented to the initiation of research activities rather than, as is more usual, to the achievement of scientific ends. Target dates can only be realistically assigned at present to anticipated staffing schedules, physical plant development and activation, and establishment of internal resources, such as animal colony, inhouse computer equipment, design and construction of technical equipment, and fabrication of highly specialized laboratory facilities.

The schedule for fiscal year 1967 calls for a staff of 66. The first increment of facilities to be completed will allow for the development of an animal colony and the availability of wet laboratory space for biochemistry, for experimental pathology and biology, as well as office space for the initiation of epidemiology and biometry studies.

Fiscal year 1968 should witness an increase in the staff to approximately 180 people and the completion of the nucleus for the permanent animal colony, as well as initiation of the first phases of research in basic and applied disciplines. During this year, the construction of the additional 30,000 square feet of laboratory space, 10,000 of which is devoted to special laboratory facilities for total body exposure experiments, should be completed and ready for installation of special equipment.

Fiscal year 1969 should witness an increase in the staff to a total between 350 and 400 people. During this year, the highly specialized equipment in the newly completed laboratory space will be installed. The epidemiology program will have completed its first phase, including the identification of selected human populations for study and the biometry program will begin to make available model systems for study in response to specific needs. General laboratory work will have proceeded in the specific areas described elsewhere in this document.

It is anticipated that during fiscal year 1970 program staff will completely occupy the interim facilities and unless an unidentified capability for expansion appears, we will be entering into a plateau period which will persist until the completion of the construction of the first units of the permanent facility. During this year, it is anticipated that the permanent facility plans will have been completed and that construction will start so that the targeted personnel goal of 1,000 people can be achieved.

Fiscal years 1971 and 1972 should witness the increasing participation of center staff in the planning and activation of the permanent facility.

Throughout the quinquennium covered here, the extramural program will be concerned with an expanding effort at developing extramural research in environmental health through its regular grants programs, centers development program, and training activities.

DIVISION/INSTITUTE CONSOLIDATION—DIVISION OF ENVIRONMENTAL HEALTH SCIENCES

[In millions of dollars]

Program element	1967	1968	1969	1970	1971	1972	1973	Total
Total, disease-oriented research								
Subtotal, specific and nonspecific disease areas								
Non-specific disease areas: Environmental health sciences	8.700	13.500	21.000	27.600	37.000	45.000	50.300	203.100
Subtotal, training programs								
Training grants	4.300	4.900	6.400	7.300	8.400	9.700	11.200	52.200
Total	13.000	18.400	27.400	34.900	45.400	54.700	*61.500	255.300

*This amount expressed in 1976 would be $105,780,000.

Mr. OBEY. Would you also give me a full report for the record on what you are doing on those asbestos experiments? You know, given the fact it is my district involved more so than others.

Dr. RALL. Yes; we shall.

[The information follows:]

BIOLOGICAL EFFECTS OF INGESTED ASBESTOS

While there has been growing concern for the past two decades about the pathogenic effects of inhaled asbestos, relatively little attention was given to the biological effects of ingested asbestos. Early in 1973, it was recognized that fairly extensive pollution of Lake Superior waters with mine residues containing asbestiform fibers was resulting in contamination of the municipal water. In addition, other sources of asbestiform fibers find their way into material which man consumes; examples are natural contamination from serpentine rock, transmission of water through asbestos cement pipes, and use of asbestos filters for such products as beer and wine.

A conference on the biological effects of orally ingested asbestos was organized and held in 1973 cosponsored by the National Institute of Environmental Health Sciences and the Environmental Protection Agency; the conference was held in Durham, N.C., November 8–20, 1973. The proceedings of this conference were published in EHP, volume 9, December 1974.

The DHEW committee to coordinate toxicology and related programs formed a subcommittee to review existing knowledge of the biological effects of ingested asbestos and recommend future research needs. This subcommittee had representation from the Food and Drug Administration, National Cancer Institute, National Institute of Environmental Health Sciences, as well as working observers from EPA and other agencies. It concluded that there was not sufficient data to determine biological effects of oral ingestion of asbestos, and it proposed that specific studies be undertaken. The subcommittee then prepared a working draft of a research protocol which was widely distributed for comments both within and without the Government. An open meeting was held on February 18, 1976, in Bethesda, Md., to receive comments, suggestions, and criticisms on this draft protocol. Based on comments received at the open meeting as well as other comments provided, the subcommittee revised its original working draft and prepared a final protocol which it again submitted to various agencies for comments. Subsequently, the National Institute of Environmental Health Sciences developed research contracts to study the effects of oral ingested asbestos in rats and hamsters. These studies are to be conducted at Hazleton Research Laboratories, Vienna, Va., and the Illinois Research Institute of Technology Research Institute, Chicago, Ill. Other research is being performed at the National Institute of Environmental Health Sciences and the U.S. Bureau of Mines.

Asbestos

The current protocol is to study two forms of chrysotile, one which has a broad range of fiber length and another one which represents a range of fibers less than 20 microns in length. In addition to the two chrysotile samples, two forms of amosite (again reflecting the broad range of fiber length as well as a second sample which is restricted to the shorter fiber length), tremolite and crocidolite will be evaluated. Great care is being given in the preparation and characterization of the asbestos material to insure that the samples are truly representative of asbestos per se.

Animal Studies

All materials will be tested in rats, whereas the two chrysotile samples and broad range amosite will also be tested in hamsters. The hamster represents the "second species"; as such, it is being fed a material that represents a serpentine and an amphibole type of asbestos. Each material is to be fed continuously in the diet at a 1-percent level. The two shortrange fiber sizes will be fed at something less than 1 percent to take into consideration the correlation of mass/fiber relationships.

All studies are to encompass the life span of the animal, which is defined as the age an animal begins eating solid food until its death. To determine newborn

effects, a segment of the study incorporates exposure by gavage from birth to weaning, followed by consumption of asbestos in the diet till death.

A portion of the study seeks to determine if there is an interaction between asbestos and a chemical known to cause tumors of the gastrointestinal tract.

Progress

The sample of tremolite has been mined and shipped to NIEHS. It is currently being characterized as to purity and exact composition by the U.S. Bureau of Mines and the Illinois Institute of Technology Research Institute.

Contracts have been let for the preparation and supply of the amosite and crocidolite samples.

Preliminary studies which determine the chemical as well as the dose of chemical to be used in the studies which measure the interactive effects of asbestos and a chemical known to produce intestinal tumors were started in September 1975.

Studies were conducted to determine if the diet which contains asbestos could be pelleted without adversely affecting the fibers. These studies are complete and indicate that pelleting can be accomplished. Use of pelleted diets will significantly reduce the potential aerosol exposure of experimental animals and research personnel to the asbestos fibers.

The portion of the studies which includes the lifetime exposure of rats and hamsters to specific asbestos materials will commence during the last quarter of fiscal year 1976.

TENTATIVE ORAL ASBESTOS ANIMAL TEST GROUPS

	Chrysotile broad range	Chrysotile short range	Amosite borad range	Amosite short range	Crocidolite	Tremolite
HAMSTERS (TOTAL, 3,100)						
Asbestos diet	500	500	500	ND	ND	ND
Asbestos diet plus chemical carcinogen [1]	350	ND	ND	ND	ND	ND
Preweaning asbestos gavage plus asbestos diet	ND	ND	ND	ND	ND	ND
Control diet [2]	500	250	250	ND	ND	ND
Control diet plus chemical carcinogen [1]	250	ND	ND	ND	ND	ND
RATS (TOTAL, 5,650)						
Asbestos diet	500	500	500	500	500	500
Asbestos diet plus chemical carcinogen [1]	350	ND	350	ND	ND	ND
Preweaning asbestos gavage plus asbestos diet	200	ND	200	ND	ND	ND
Control diet [2]	175	175	175	1/5	175	175
Control diet plus chemical carcinogen [1]	250	ND	250	ND	ND	ND

[1] Numbers may be adjusted pending results of dose ranging studies to determine 15±5 percent tumor incidence in controls.

[2] Control allocations are descriptive only; it is expected that experimental response will be evaluated against total controls (1,000). Subsets of control will reflect temporal differences in commencing phases of study which is expected to be aggregates of 250 to 350.

ND—Not done.

Mr. OBEY. Also, NCI is spending about $200,000 per chemical to determine carcinogenessi. You are spending $3–4 million. Why is it so expensive?

Dr. RALL. There are a number of reasons for that. We talk about asbestos as if it were a single entity. There are a number of fiber forms all of which we call asbestos. We will be looking at four totally separate fiber types of asbestos, chrysotile, amosite, crocidolite and tremolite.

One of the main problems is the relationship between the length and diameter of the fiber and its toxicity. Because this is such a critical area, we are planning on doing two fiber sizes.

Mr. OBEY. To do what?

Dr. RALL. Two fiber sizes—a long, skinny fiber and tiny fiber.

What is in Lake Superior is the small fiber—very short ones. We really want to test that fiber size since much of the exposure to asbestos is really over the lifetime—for instance a child in Duluth drinks the water from almost the moment he is born. We will have separate groups of animals exposed to asbestos from weaning on.

So all of this means extra groups. If you go to each group, not the entire experiment, the figure is about the same. It will cost us a couple of hundred thousand for one group. We are doing about 15 different experiments under one umbrella.

NCI BIOASSAY PROGRAM

Mr. OBEY. Something has been troubling me a little since Dr. Rauscher testified last week. Evidently the Cancer Institute is testing about 150 chemicals a year, spending over $35 million on those tests. Those chemicals being tested are suspected of causing not just cancer but other kinds of diseases as well, but it isn't the responsibility of NCI to check into these results as they might relate to diseases other than cancer.

To your knowledge is anything being done under which somebody else could piggyback with NCI, so when they are finished testing animals for the results they are looking for, somebody else is checking them out for possible implications for other diseases?

Dr. RALL. I have begun at least preliminary discussions with the Cancer Institute with this very idea in mind. For instance, they do 90-day dose-finding studies to be sure that their lifetime study is at a proper dose. These animals would be very, very useful to look at for other forms of chronic toxicity, liver, kidney, and so forth. My preliminary discussions with NCI have been very hopeful that we can work out something. It probably would cost $2 or $3 million a year to really be able to do this properly.

Mr. OBEY. What kind of time frame are you talking about?

Dr. RALL. Sometime within the next calendar year if everything could be worked out so that we could begin to find enough competent toxicologists to look at these animals and begin to find out what else is needed.

Mr. OBEY. It just seems to me if we are spending $35 million for those tests and not following up on the other aspects of the tests, you are really wasting an opportunity that, with a couple million dollars, would make it well worthwhile.

Dr. RALL. I think that is absolutely true.

RESEARCH PROGRAM

Mr. OBEY. Your justification doesn't really break out what is going on in your inhouse research program. Would you submit for the record what each division does and the position levels they had in 1973, 1974, 1975, and 1976, and the President's request for 1977, and what each would have if you received 50 positions over the 1976 level.

[The information follows:]

National Institute of Environmental Health Sciences

Permanent Full-Time Positions

	1973 Actual	1974 Actual	1975 Actual	1976 Estimate	1977 Budget Estimate	Level Reflecting 50 Positions over 1976
Intramural research programs:						
Office of scientific director	---	---	---	2	2	2
Environmental biometry branch	7	8	8	11	9	12
Environmental biophysics branch	11	9	11	10	10	12
Environmental mutagenesis branch	17	25	22	27	21	38
*Environmental toxicology branch	---	32	30*	32*	28	43*
Pharmacology branch	25	22	22	22	19	28
Epidemiology	---	---	---	4	---	7
Research resources:						
Office of associate director	---	---	---	2	2	2
Environmental biology and chemistry branch	42	66	66	71	66	81
Research services branch	24	26	30	29	26	31
Office of administrative management	24	24	23	26	23	28
Office of extramural program	12	12	11	13	13	13
**Office of director and office of program	15	12	17**	22**	19**	24**
Branches/Activities that have been abolished to free resources to allocate to other areas:						
Analytical and synthetic chemistry branch	17	---	---	---	---	---
Pathologic physiology branch	32	---	---	---	---	---
Office of associate director for scientific information and communications	4	1	---	---	---	---
Total, NIEHS	230	237	240	271	238	321

*Includes behavioral toxicology

**Includes Technological Surveillance Activities, and secretariat services for the DHEW Committee to Coordinate Toxicology and Related Programs

Activity Descriptions

Intramural Research Programs:

Office of Scientific Director -- Plans and directs the Institute's laboratory research programs.

Environmental Biometry Branch -- Fulfills a dual mission, functioning both in a service capacity to the intramural program and as an applied research group. Statistical support for the Institute is provided mainly for the design of experiments and in the analysis of laboratory data.

Environmental Biophysics Branch -- Plans and conducts studies of the effect on humans of physical factors in the environment such as ionizing and non-ionizing radiation, noise, heat, humidity, and vibration; and advises and collaborates with other Institute staff on studies involving the interaction of such physical stressors with other agents of concern.

Environmental Mutagenesis Branch -- Objective of this program is focused on evaluating and defining risks to both human somatic and germinal tissue resulting from exposure to genetically active environmental chemicals.

Environmental Toxicology Branch -- Efforts are directed toward understanding mechanisms of toxicity. Special emphasis is placed on environmental problems relating to reproduction and development. These basic studies contribute to development of better and more effective test procedures to predict toxicity in humans.

Pharmacology Branch -- Concerned with understanding mechanisms by which environmental pollutants and effectors cause toxicity, and development of better test systems for detecting and evaluating early toxic effects of environmental chemicals and for extrapolating from animal test systems across species and to man.

Epidemiology -- Studies aimed at identifying factors associated with human disease through study of effects in populations exposed to environmental agents in a real life setting; and at testing hypotheses generated by experiments on laboratory animals.

Research Resources

Office of Associate Director -- Plans, develops, and provides centralized Institute research and support functions.

Environmental Biology and Chemistry Branch -- Focuses on three objectives: to maintain collaborative support laboratories in the disciplines of chemistry, inhalation toxicology, microbiology, pathology, histology and electron microscopy, and veterinary medicine; to program and coordinate experimental animal procurement, housing and utilization within the Institute; and to conduct research appropriate to the capabilities of Branch laboratories.

Research Services Branch -- Provides and coordinates Institute facilities support services.

Office of Administrative Management -- Plans, develops, directs, and evaluates administrative and staff support.

Office of Extramural Program -- Responsible for the scientific and administrative management of the Institute's grants programs.

Office of the Director and Office of Program -- Provides for the planning, direction, management, and coordination of all Institute activities. Also, provides for technological surveillance activities, which attempt to identify existing or potential hazards to man and the environment from chemicals of present or future use. Additionally, provides secretariat services for the DHEW Committee to Coordinate Toxicology and Related Programs.

RESEARCH PROJECTS

Mr. OBEY. Could you also submit for the record a summary of the research projects you have been involved in for several years.

[The information follows:]

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NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Research Advances
1970 - 1975

During the last five years, NIEHS has been involved in research on a variety of environmental health problems, many having major significance of man's health.

Dioxin

One example concerns the contaminant "dioxin" (2,3,7,8-tetrachlorodibenzo-p-dioxin or TCDD) found in commercial samples of the once commonly used herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid). At first scientists believed 2,4,5-T itself affected the development and viability of mouse and rat fetuses. Following work done by an NIEHS team, however, a contaminant in the 2,4,5-T was discovered to be the real culprit. This contaminant was dioxin or TCDD. TCDD has since been revealed as one of the most toxic substances known to man. After the NIEHS research was reported, the Environmental Protection Agency restricted use of 2,4,5-T.

Subsequent studies by NIEHS researchers revealed an increased susceptibility in mice to bacterial infection as a result of exposure to TCDD. These studies showed that extremely low levels of TCDD, which do not produce clinical or pathological change, still have the capacity to affect host defense. These findings are significant in that humans may be exposed to environmental contaminants such as TCDD in minute quantities and, therefore, may be rendered more susceptible to certain types of infectious agents.

Bis (Chloromethyl) Ether

Work done by a team of scientists supported by an NIEHS center grant at New York University Institute of Environmental Medicine revealed a significant hazard to human health which could then be controlled or removed from the environment. This hazard was associated with bis (chloromethyl) ether, a colorless chemical that is one of a family of organic chemicals commonly called halo ethers. These compounds are used in large quantities in the chemical industry for polymerization and stabilization of polymers.

These investigators suspected on the basis of the chemical structure of the bis (chloromethyl) ether that this compound might be carcinogenic, capable of causing cancer. Testing the compound in mice and rats supported this theory. Bis (chloromethyl) ether is a potent carcinogen when applied to the skin of mice or when injected in mice or rats. In fact we now know that very small concentrations in the air may cause a significant increase in certain kinds of lung cancer. Thus, we cannot be reassurred by the knowledge that most of these compounds are present in the environment at very low concentrations. And the fact that later testing showed mice may develop lung tumors after inhalation of very low concentrations of the compound is particularly important because workers in the chemical industry probably have been exposed to fumes of the compound.

At this time, it is impossible to determine how many people have been exposed to either bis (chloromethyl) ether or its related compounds. At least 3000 men are known to have been exposed in the chemical industry. Federal agencies and the industries involved are keeping these men under close surveillance as a group with above average expectancy of developing cancer.

Studies by the NYU team on the health of workers in six chemical plants have shown that workers run a two-and-one-half to three times greater risk of lung cancer than a control groups of people not exposed to bis (chloromethyl) ether. Since these studies, scientists have found an excessive number of cases among chemical workers in Germany and Japan. In one group, all the lung cancer deaths occurred in workers subjected to heavy exposure to the chemical for five or more years.

Because almost the entire production of bis (chloromethyl) ether is used by the corporation that makes it and because very little is sold outside the plant, bis (chloromethyl) ether until recently appeared to be mainly an occupational health problem and not a general environmental health problem for the entire

population. Not long ago, however, several halo ethers appeared in the Ohio River water, Rhine River water, and a variety of other rivers that flow through major industrial areas. These compounds were found to be present in discharges from chemical plants in the vicinity and subsequently were detected in municipal drinking water. Effective steps are being taken by regulatory agencies to limit such exposure, as well as exposure in the work place.

Asbestos

Another problem that concerns NIEHS is how to protect the population from hazards associated with compounds we already are using that seem essential to our everyday living and continued economic development. This dilemma is sharply apparent in the cause of asbestos. It is now clear that failure to carry out research on this problem in the 1930's and 1940's left us with a terrible legacy of perhaps tens of thousands of asbestos-related deaths.

Approximately nine years ago, the NIEHS began to support rather extensive research on asbestos. As a result, we now know the consequences of uncontrolled industrial use of the material. Since 1973, the National Institute of Environmental Health Sciences has been supporting an Environmental Health Sciences Center which concentrates on asbestos research. This Center is located at Mount Sinai School of Medicine, New York, and is under the direction of Dr. Irving J. Selikoff, a pioneer in asbestos epidemiology. It was to Dr. Selikoff, incidentally, that the Environmental Protection Agency turned recently for recommendations when confronted with asbestos contamination of drinking water in Duluth, Minnesota.

Recently Center personnel reported that analysis of representative samples of spackling, patching, and taping compounds has shown that some contain asbestos minerals as well as other potentially harmful substances. Measurements suggest that home repair or construction work involving use of such materials may result in exposure to dust at concentrations sufficient to produce disease.

Fifteen representative samples of consumer spackling and patching compounds and ten of industrial drywall taping compounds were analyzed for asbestos mineral content. Four of the spackling and patching compounds were purchased at hardware stores in the New York City area in 1972 or earlier, and the remainder in January 1974.

Spackling and drywall taping compounds consist of finely-grained white powder or premixed pastes. Although Plaster of Paris is supposedly the major constitutent, other light-colored materials including clays, micas, quartz, talc, and ground limestone supplement or replace the plaster in many formulations. Additionally, chrysotile asbestos is added to some products, apparently because these minute fibers act as reinforcing agents.

Analysis of the 15 consumer spackling and patching samples has shown that 5 contained appreciable amounts of chrysotile or other asbestos minerals, as did 9 of the 10 industrial products. Many contained substantial amounts of quartz, talc, and other minerals. Once embedded in the lungs, quartz or silica particles--like those of asbestos--may never be removed. They can produce chronic obstructive and fibrotic diseases after prolonged exposure. Talc also can produce pulmonary fibrosis.

Air samples obtained during the use of asbestos-containing spackle compounds were analyzed and showed concentrations frequently in excess of the current occupational standard for permissible asbestos exposure levels. Fiber counts measured during mixing for example were found to be 7-12 times greater than the standard. Detectable fiber concentrations were found in adjacent rooms during mixing, and fibers were still suspended in the room air at least 15 minutes after mixing had ceased.

These findings suggest the possibility of significant asbestos exposure during home construction repair. Additional work by the Center personnel suggests that members of the entire household or other occupants of a building may also inhale asbestos fibers. This could occur during mixing, sanding, or cleaning up of debris.

These results are alarming when considered in relation to other evidence being accumulated by the Mount Sinai group that indicates that far less than the intense exposure of the work environment is capable of producing asbestos-related disease. X-ray examination of 210 family contacts who lived with the men who produced asbestos insulation at a Paterson, New Jersey, plant from 1941 to 1954 has shown

that 40 percent have the kinds of abnormalities in their lungs common to asbestos workers. In some cases, the worker had been at the Paterson plant for only a few days.

Thus, it appears likely that the use of spackling, patching, and taping compounds containing appreciable levels of asbestos minerals in home repair work may expose the user, and other members of the household, to concentrations of asbestos that may lead to disease.

Ozone

Some scientists are warning that a group of aerosol propellants called chlorofluorocarbons may be damaging the earth's protective layer of ozone. Chlorofluorocarbons, used under pressure to eject sprays, are found in many household products including some hair sprays, deodorants, antiperspirants, and pharmaceuticals. They are also used as refrigerants.

Some experts have suggested that chlorofluorocarbons break down under the influence of sunlight in the earth's upper atmosphere, releasing free chlorine that then acts to reduce the abundance of ozone. Many believe the depletion of ozone, which absorbs the most lethal wavelenghts of ultraviolet radiation, could lead to a worldwide increase in skin cancer incidence.

Since the aerosol sprays came into extensive use, a sharp increase in the amount of chlorofluorocarbons in the upper atmosphere has been observed. This finding has triggered concern about the possibility of serious environmental health hazards resulting. A ban on the use of chlorofluorocarbons in aerosols is currently under study. NIEHS has supported much of the research that has made it possible to begin assessing the effects of changes in the ozone shield on man's health. Currently NIEHS scientists are working with the Council on Environmental Quality and the National Science Foundation, advisory groups to the President, to determine the extent and environmental effects of possible changes in the earth's protective ozone shield.

Ozone and Nitrogen Dioxide

Another example of NIEHS work on ozone concerns studies underway virtually since the opening of the Institute in 1966. These studies have now uncovered strong evidence that ozone and another pollutant in our environment--nitrogen dioxide--are contributing, if not primary, causes of pulmonary emphysema and chronic nonspecific pulmonary disease. In addition to protecting us from the most harmful of the sun's rays, ozone can adversely affect our health.

A part of the picture establishing the sequence of events of ozone and nitrogen dioxide toxicity was provided by NIEHS grantees who produced an experimental facsimile of human emphysema in rats. They also showed that ozone is approximately twenty times more toxic than nitrogen dioxide. In fact within a few hours of exposure to less than 0.5 part per million ozone--a concentration readily achieved at peak traffic hours in some urban areas--considerable reaction in the lung becomes apparent.

Other grantees found that the focal points of damage at all levels of exposure to ozone in the rat are the small airways of the lung. Still others discovered that the carbonyl compounds that begin to circulate in the blood stream shortly after ozone exposure may serve as a basis for early detection of ozone damage by simple chemical techniques.

While all these studies establish rather clearly what happens in ozone and nitrogen dioxide induced disease, the research of other NIEHS grantees encourages the belief that much of the damage induced by these two pollutants at low levels can be prevented and perhaps reversed in the early stages. Some grantees have demonstrated that lipid antioxidants, particularly vitamins A and E, protect against ozone toxicity; others that certain minerals, particularly zinc, may be useful for this purpose. These findings are particularly important as emphysema has led to death for an increasing number of people since 1950, and chronic nonspecific pulmonary disease is now a leading cause of disability among adult males.

To complete the picture of ozone and nitrogen dioxide toxicity, clinical evaluations must be made of vitamins A and E, zinc, and other compounds, as well as combinations of these in test animals and eventually human populations at risk of toxic exposures.

DES

NIEHS studies with DES (diethylstilbestrol), a synthetic hormone, have emphasized the unique sensitivity of the embryonic period to chemical insults that may result in infertility and perhaps cancer later in life.

Although many compounds are continuously introduced into our environment, few of them have been examined for their potentially toxic effects on reproduction and development. Virtually nothing is known about the effects of exposures to common drugs and chemicals occurring before birth on the development of the offspring after birth.

NIEHS scientists have been using mice to study the effects of environmental agents on reproductive tract function. In their work with DES, a common environmental chemical currently used as a livestock food additive and "morning-after" contraceptive, they demonstrated that prenatal or before birth exposure to DES adversely affects the reproductive capacity of the female offspring. This effect is dose-related and is due in part to the relative inability of the female offspring to ovulate. During the prenatal period oocytes (reproductive cells) undergo division in man and in laboratory rodents, and at that time they are especially susceptible to chemical intervention.

These researchers also found that the male offspring are sterile following prenatal exposure to certain doses of DES. Test results suggest that DES affects the same embryonic tissues in both male and female fetuses and results in postnatal defects in both sexes. The reproductive tracts in the prenatally drug-exposed offspring have lesions which include changes in cell types and/or tumors.

In light of these results in rodents, the incidence of genital tract abnormalities in young men whose mothers were treated with DES during pregnancy may be of clinical importance. In fact, researchers at the Chicago Lying-In Hospital recently reported reproductive tract abnormalities among sons born to women who had received DES.

The results of the NIEHS studies may be pertinent to the development of an animal model to study the reproductive tract lesions reported in young women whose mothers had been given DES during pregnancy to prevent abortion. Such a model could permit more rapid testing of the compound's teratogenic acitivity and could hopefully lead to the development of a way to predict for these toxic effects.

Mutagenic Agents

Discovery of cancer among workers exposed to vinyl chloride (a gas from which polyvinyl chloride is made) emphasizes the need for better ways to evaluate the potential hazards in the environment prior to man's exposure. These hazards include mutagenic agents or agents that cause genetic damage. This damage may take many forms. It may result for example in chromosome alterations that can cause spontaneous abortions or an increase in inheritable disease such as hemophilia.

Development of short-term qualitative tests to evaluate the thousands of man-made chemicals already in the environment that have never before been tested for mutagenic activity is the focus of effort by a group of NIEHS scientists. These NIEHS researchers have been working on *in vitro* or test tube techniques for metabolic activation which would allow mammalian metabolites (often the active mutagens) to be tested, as well as the original compound. Through use of such techniques the necessity for using whole animals for screening could be avoided and reserved for obtaining quantitative data required for risk confirmation and evaluation.

Short-term tests for determining mutagenic acitvity 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. Because exploratory testing of environmental chemicals and other compounds is turning up new examples of genetic activity in products in widespread use this capability is needed. For example almost all commercially-available hair dyes were recently discovered to be genetically active in some of the newly-developed short-term tests. The potential hazard for the estimated 20 million people in this country alone who dye their hair is not yet known. NIEHS has already initiated studies to determine whether hair dyes cause genetic damage in other experimental organisms in order to better evaluate the risk for man.

The short-term tests may offer answers in another area of concern. While the relationship betwen mutagenicity and carcinogenicity (cancer-causing ability) is still a matter of considerable scientific controversy, contract work--supported by the National Cancer Institute 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.

These tests also offer a potential solution to a 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 that a valuable product is carcinogenic in the traditional two-year assay on laboratory animals. Utilization of short-term tests for mutagenicity offers a rapid, inexpensive mechanism for weeding out products with potential adverse effects early in the development process.

The compound AF-2, the nitrofuran derivative widely used as a food preservative in Japan beginning in 1965, exemplifies the capability of this approach. AF-2 was first determined to be mutagenic in the newly-developed short-term tests over a year ago. Much later it was found to be carcinogenic in mice. Vinyl chloride also has been found to be genetically-active in these tests. Had this activity been determined years ago the vinyl chloride hazard to industrial workers and the population in general might have been avoided.

Vinyl chloride's genetic activity in these tests reemphasizes the need to develop better methods for determining effects of exposure to mutagenic chemicals on man himself. Additionally, compounds structurally similar to vinyl chloride must be studied to learn if they are genetically active in these tests. If they are, the effects of exposure to them must be evaluated. Currently NIEHS investigators are studying vinyl bromide, a compound structurally similar to vinyl chloride, which is used to make flame resistant fabric. Because this fabric can save lives NIEHS must determine whether vinyl bromide may be highly toxic and, therefore, unsafe to use without at least careful containment.

The difficulty with a situation such as the discovery that AF-2 is a potential mutagen and carcinogen is our inability to evaluate th 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 the long-term effects, such as an increase in cancer incidence, would not be expected to appear for a least 15 to 20 years. In such situations we may have the illusion of safety based on our inability to test rather than on sound scientific data. For this reason NIEHS scientists are giving high priority to the development of a capability to perform meaningful tests on man himself a short time after the exposure has occurred to determine and evaluate effects of inadvertent exposure to environmental compounds.

Noise

Other NIEHS research that may have an impact on a segment of our population began with research on noise. While developing techniques to evaluate how the ear handles acoustical information, one research team developed a device to impart complex signals, including speech, to the cochlea, the essential organ of hearing. This device may have important implications for people with certain kinds of hearing losses. No device, however, can greatly help people with severe sensory-neural losses resulting from exposure to excessive noise or certain drugs called ototoxic drugs. These losses are characterized by permanent destruction of a portion of the sensory cells and nerve endings.

By comparison with ordinary high-fidelity standards, conventional hearing aids are poor sound transmission devices. Further, because of the need for using a tiny acoustical diaphragm to generate sound in the hearing aid, great improvements are unlikely in the near future. To ask such a small diaphragm to perform acceptably over a wide amplitude and wide frequency range is asking it to perform the impossible and buck many of the laws governing sound generating equipment. These laws say that a fairly large vibrating object is required for efficient production of sound, particularly in the low frequencies.

In addition to the size problem, there are problems of feedback and squeal when the microphone and speaker are placed close together. Further, significant distortion is usually found when production of high-intensity, wide-frequency sound is attempted from small acoustic sources.

Doctors, called otologists, who specialize in ear problems have long thought that implanted devices might be capable of imparting sound directly to the inner ear by driving the ossicular chain, the small bones of the middle ear. They thought this could be done by placing a tiny direct-contact transducer at the ossicular chain. But until now no one has extensively examined the fidelity possible by using such devices.

NIEHS scientists have developed such a device, called a piezoelectric transducer. When in direct contact with the ossicular chain, it can impart highly defined signals to the cochlea. Experiments with research animals have shown this device produces the same order of fidelity as possible by the normal method of hearing.

2,4-D

Other studies underway at the Institute may help determine which marine species are safe for human consumption. These studies have focused on the way various marine species, including the dogfish shark, modify and dispose of the widely used herbicide 2,4-D (2,4-dichlorophenoxyacetic acid), a contaminant in the ocean. The dogfish shark makes an excellent model for studying 2,4-D as it has a simpler, but essentially similar, metabolic factory to man's. Its liver is less complex, yet the biochemical changes that take place in it seem to be comparable to those occurring in the human liver. In the NIEHS studies 2,4-D was found to be excreted much more slowly by dogfish shark than by the laboratory rat.

By showing how the body's handling of substances differs in various species we may be able to explain the variability in the period that environmental contaminants stay in marine species. This could be an important factor in determining which are safe for human consumption. We need to know which species store which pollutants so human exposure can be prevented. Then we can avoid future problems like the sword fish-mercury scare of the 1970's.

Styrene Oxide

We may also be able to protect certain segments of our population from risk linked to exposure to specific pollutants if we can develop information on how the lung handles pollutants. The lung is the primary site of chemical toxicity, so the way it processes pollutants may play a significant role in the overall toxicity of chemicals.

To develop this information scientists at the Research Triangle Park Institute have been using a model system built around an isolated perfused lung. This system permits the study of rat and rabbit lungs outside the body while these organs are functioning normally for a time. It keeps the lung alive in the sense that it operates as it would in the body. It also allows scientists to be sure that effects they are measuring are all happening in the lung. In this way we can understand the means by which the lung copes with inhaled substances.

One example of the use of this model system is NIEHS research on styrene oxide. This compound is a metabolite formed from styrene, one of the most widely used chemicals in the polymer industry. It is relatively safe to use and yet it is a good model for studying the metabolism or processing of even more toxic chemicals, such as polycyclic aromatic hydrocarbons, pollutants known to cause cancer.

In studies with styrene oxide scientists have shown that the amount of glutathione in the lung may be an important factor in whether styrene oxide is made less toxic, a process referred to as detoxication. When environmental agents enter the body body, the first stage of processing they undergo leads to the formation of metabolites, some of which are more toxic to mammalian systems than the original contaminant. Some of these metabolites then may be detoxified by other systems in the body. Glutathione, a naturally-occurring substance in the body, is capable of making metabolites less toxic.

As glutathione concentrations in the lung decrease during the lung's continuing exposure to styrene oxide, NIEHS studies show swelling or edema. If the concentrations or glutathione is the limiting factor in the detoxication of styrene oxide, then it may be possible to protect workers exposed to this chemical by adding

by adding supplementary compounds to their diets that build up glutathione levels.

Estimating Human Risk

The primary goal of all NIEHS research is to apply the findings to the human exposure situation and prevent disease. The public cannot affort to wait for clinical manifestations of diseases to appear before the search for potential causative agents begins. Because the latency period (time from initial exposure to effect) associated with such categories of disease as cancer and genetic disorders often ranges from ten years to two or more generations, a significant proportion of our population may be exposed to irreversible deleterious effects if we wait for sufficient human data to accumulate to conduct risk assessment.

Rather than waiting, decisions regarding acceptable levels of various environmental agents are being based on information derived from animal experiments, where cancer latency periods are reduced to intervals of 12 to 18 months and entire lifetimes are covered in a two to three year time span.

The procedure generally used to estimate risk associated with human exposure to a potental environmental carcinogen or cancer-causing agent usually begins with determining the carcinogenicity of the specified agent at relatively high doses in laboratory animals. The observed risk is then extrapolated or projected down to human exposure levels and equated to human risk by some conversion factor.

One of the major obstacles to developing realistic animal models for predicting human response is the problem of extrapolating to low dose levels, a procedure involving use of a mathematical model of the carcinogenesis process. Because two or more models may nearly coincide in the experimental dose range but yield widely divergent results in the actual range of human exposure, the model chosen for extrapolation is critical in determining the order of magnitude of the resulting estimate of human cancer risk.

Recently a team of NIEHS researchers has been examining probabilistic and mathematical models for extrapolation. They have emphasized models that specify possible biological mechanisms of carcinogenesis and have evaluated the importance of background incidence of disease and tumor induction in risk evaluation.

Their findings have been used to develop guidelines for selecting sample size and dose levels in animal carcinogenesis experiments. One of the design principles delineated in their effort indicates that increasing the number of animals beyond a certain level does not appear to bring about a proportional increase in the sensitivity of the test.

These efforts will continue so that the potential risk linked to exposure to environmental agents can be more realisticaly evaluted and so that human well-being can be protected.

MUTAGENESIS TESTING

Mr. OBEY. Last year you talked about mutagenesis testing. Where are you on that? Do you think they are now beginning to be reliable enough to be a good indicator of what chemicals might be carcinogenic?

Dr. RALL. I am convinced that they are now in a position to be used as a screening method for environmental chemicals. Our mutagenesis group is in the process of developing a contract to set up a testing procedure to begin to look at the feasibility of in essence screening environmental chemicals for these mutagenetic and other similar effects.

I think we are ready now to begin.

Mr. OBEY. What is the current cost of doing those types of tests?

Dr. RALL. A single test, which is not enough, costs about $200. You probably would want to set up a battery of about 10 of them so that for 1 compound something in the order of $2,000, maybe up to $4,000 would be reasonable.

Mr. OBEY. You mentioned you were testing vinyl bromide and asbestos. NCI is spending a lot of money on chemicals. NIOSH, EPA—you name it. Even with all that activity we are still only testing a very small portion of the chemicals in the environment.

I have been asking you and everybody else for the last 2 or 3 years how you decide which chemicals are the right ones to look at. Evidently NCI and OSHA have contracted with Stanford to make some estimates for them. But we still don't know very much about the chemicals, so I get the feeling really as a layman that we still don't know very much about it.

With this method of testing chemicals that you are developing—Rauscher said we had something like 10,000 chemicals in major production—couldn't you use this kind of system to really go at that thing in a massive way? What is practical? How many chemicals, once you are determined there is a sensible way to go, can you test roughly in 1 year?

Dr. RALL. I think if everything went well you could end up testing at least 2,000 or 3,000 chemicals a year and being able to keep track of the system, so that you knew what was going on.

We are now at the stage of being able to initiate a rather modest contract to get at the feasibility of this. In other words, can we go out and get a contract set up that will do this? We think we can. We can do it in the laboratory. Other people can do it in their laboratory. This is sort of the pilot plant stage of production.

Can it be done in a commercial laboratory on a routine basis?

I think we probably can, I think our plan for this year is to begin that with the idea that next year we would have a system in place that could begin to test fair numbers of random environmental chemicals.

Mr. OBEY. What would be fair numbers?

Dr. RALL. I think the first year you might want to talk about 200 or 300 because you will always have bugs in getting a system to work. After that I think you could go up to 1,000 or so.

Mr. OBEY. What would the price tag be over a 3-year gear-up period on something like that? How many chemicals within the 3 years could you have effectively tested?

Dr. RALL. I think it would probably cost about $1 million the first year to really set the system up to be sure it works. It would cost a lot of our in-house time too, and our scientists would have to be very much involved in this to be sure it was running well.

Mr. OBEY. What will that million be used for?

Dr. RALL. Mostly setting up contracts to do the tests and monitoring them to be sure that they were valid and reproducible and good tests.

Then I think we would want to set up a system to couple this very directly and closely to NCI for input into its program and into the regulatory agencies such as EPA, NIOSH, and OSHA, because I think they should have immediate access.

The next step which would also be important is for the NCI bioassay program to take not only compounds of real environmental interest but clear negatives and clear positives to check it out in their system to see how these two relate. This would be a very critical step, and I think in 3 or 4 years I would hope we would have a very much more rational system for testing compounds.

Mr. OBEY. If we are going to do it as you say, really going to have an aggressive effort on it, you say it would cost a million the first year, for the next 2 years, what kinds of costs are you talking about?

Dr. RALL. In the order of a couple million a year. A lot of that depends on how well the first year goes.

Mr. OBEY. Then how soon could we expect some specific test results to start coming in?

Dr. RALL. I think you would have specific results the end of the first year; certainly the second year.

Mr. OBEY. How about by the end of the third year?

Dr. RALL. Perhaps as many as 4,000. Really a significant fraction of those have never been tested before.

Dr. FREDRICKSON. I think it is very important to point out that confirmation of the comparability of these two kinds of statistics, the mutagenesis data and the bio assays for carcinogenesis, still remains to be done to the satisfaction of all involved. That is the big question. In order to make this effective one would have to carry out a certain number of bio assays on compounds that had negative or positive mutagenic tests in order to be sure of the correlation. A great deal of money will be involved in that.

Mr. OBEY. What kind of costs are you talking about then?

Dr. FREDRICKSON. I think you would have to select out of the number of positive or negative mutagenesis tests, and run those in the current costly and inconvenient bioassay program. It would cost roughly $100,000, or more, per compound to get this confirmatory information in a sample of the mutagenesis test results.

Mr. OBEY. What kind of sample do you think you would need before the tests would be proven out?

Dr. FREDRICKSON. It is a little difficult to be sure because different classes of compounds may be different in their ability to give a positive answer in one test and not in the other.

If you were to test a thousand compounds for mutagenesis, one would certainly want to test a hundred of those, at least, for carcinogenesis. I suppose we are talking about, then, the need for another hundred times $100,000 and, over a 3-year period because the bioassays take much longer than the mutagenesis testing.

I think we might be able to develop some more exact figures but those extra costs for confirmation had better be included.

Mr. FLOOD. Mr. Roybal?

DUPLICATION AND LIAISON—OTHER INSTITUTES

Mr. ROYBAL. A few days ago we were told that it is now believed that most cancer is caused by chemicals. This brings up two questions.

If each Institute that testified before you explores environmental factors that relate to the cause of diseases, what does that leave you to research?

Or put another way, aren't you duplicating research that is or should be going on at the other Institutes?

What type liaison have you established with the other Institutes to insure that duplication does not occur and that results of your research are shared?

Dr. RALL. Each of the other Institutes has responsibility for research on the causes of a disease or group of diseases. Accordingly, they view environmental factors as just one possible causative factor in their area of responsibility. We, on the other hand, are concerned not so much with the specific disease endpoint as we are with the process by which these environmental agents are taken up by the body, modified, used, and ultimately excreted. In the case of an environmental agent which has toxic effects, there may be multiple disease endpoints. For example, cancer and neurological damage. Thus, we frequently provide a bridge between the narrower categorical interests of the other Institutes. In addition, we believe that our approach is critical if we are going to assist the regulatory agencies in their efforts to develop effective control measures.

We have a wide variety of liaison activities with the other Institutes which occur at several levels.

First we carry out formal liaison with these Institutes through formal groups like the NIH Institute Directors Group and the Scientific Directors Group. Second, we consult with them on problems in which we have particular competence, and likewise invite them to consult with us on similar matters. And third, the NIH is in fact a community of scientists and there is an enormous amount of communication among its scientists. When I was a working level scientist in the Cancer Institute, I frequently collaborated or consulted with scientists in other Institutes.

PREMARKET TESTING

Mr. ROYBAL. You indicate that chemicals are a major cause of disease. You took PCB off the market. We have had a Kepone scare. Does this indicate that we should test all new chemicals before they are put on the market or before workers come in contact with them?

Dr. RALL. First off, Mr. Roybal, in order to clarify the record neither we nor any other Federal agency has removed the PCB's from the market. We have not, because we are a research not a regulatory agency, and we have no enforcement powers. Second, current Federal law only reaches substances like the PCB's in terms of the hazard either in the work place, its end product use, or as a pollutant in air and water. However, the thrust of your question is most valid.

As you know the Congress currently has under consideration, legislation which would control so-called toxic substances. This legislation,

which has administration support, has passed both Houses of Congress in each of the last two Congresses, but has died in conference. It is my strong view that such legislation is vitally needed.

TECHNOLOGICAL DEVELOPMENT

Mr. ROYBAL. Do your findings about chemicals mean that we must slow down or stop technological development because of possible danger to our health?

Dr. RALL. In my view the issue is not one of slowing or ceasing technological development, but rather is one of learning to live with our technological ingenuity. Thus, clearly we must be more careful about evaluating the potential hazard of a new substance or the new use of an existing substance, before it is put into the market in large volumes. Further, we must be more careful in our evaluation of the need for new compounds. If we can take these actions responsibly, then I believe we can continue to take advantage of our technological genius and harness it to the advantage of all.

OZONE LAYER

Mr. ROYBAL. Did you do any studies concerning the Concorde's effect on the ozone layer? What did you find?

Dr. RALL. This Institute did not do any studies concerning the effect of supersonic aircraft on the ozone layer. However, the National Academy of Sciences was very concerned about this particular problem and evaluated all facets of the potential depletion of the ozone layer in the stratosphere. Their report will be published shortly. The results indicate that a limited use of supersonic aircraft will hardly make a dent in the persistence and level of the ozone layer in time to come. They are, of course, not willing to say what would happen if the supersonic transports were to multiply to any major extent.

Mr. ROYBAL. We have heard that the ozone layer is being depleted. Is this true? How extensive is the depletion? What effect will it have on our citizens?

Dr. RALL. As yet it is not established that the ozone layer in the stratosphere is being depleted by fluorocarbons. On theoretical grounds as well as on laboratory data mimicking stratospheric conditions, however, it is likely that any decrease in the ozone layer could result from a free radical reaction between chlorine and ozone giving rise to oxygen and thus destroying the ozone. In this process the chlorine remains capable of further destructive action on the ozone. The compounds that could give rise to chlorine in the stratosphere are limited to those stable enough to reach the stratosphere. This means, therefore, they do not find a sink prior to reaching the heights where light energy can break the molecule that liberates chlorine atoms. The compounds most likely to present a problem are some of the simple fluorochlorinated hydrocarbons, such as Freon 11 and 12 as well as carbon tetrachloride. They are highly stable gases or readily vaporized liquids and do not have a sink in the atmosphere that would tend to trap them.

These compounds have been detected in the stratosphere, so the anticipated reaction with ozone could occur. Measurements of the ozone layer have been made since 1960 in various regions above the

Earth. Between 1962 and 1970 it was found that in most areas there has been an increase in the ozone layer rather than a decrease; but between 1970 and 1972 there generally was a decrease. This does not suggest the problem has already produced an effect that could be considered disastrous, nor do we know precisely whether all factors regarding the ozone layer are known—particularly since we have no complete explanation regarding specific changes in one area compared to another over the last 15 years.

As an example, between 1962 and 1970 when the ozone layer increased by 8 percent in European Russia, there was only a 1-percent increase in Japan. We do not have any explanation for these differences; but we do know that different ozone layers exist for different areas. These are generally greatest in the polar regions and lowest at the equator. The difference between the equator and the polar area is very great indeed. The layer at the equator is only 60 percent of that at the polar region. With such large differences caused by factors outside the Earth, it is very hard to predict what impact the fluorocarbons will have on the ozone layer.

The particular interest our Institute has in the problem of ozone depletion relates to the possibility of increases in skin cancer. This is an important problem because cancer of the skin has been found to be more frequent in skin of people, such as farmers, sailors, and pale-skinned people living in tropical areas, who are exposed to the elements. Skin cancer could definitely be correlated with exposure to greater amounts of sunlight. The Sun's energy that is responsible for skin cancer is that of wavelengths between 280 and 320 nm. These are the wavelengths that would be most affected by changes in the ozone layer. New equipment for monitoring, metering and measuring irradiation of experimental animals and man has been developed by an NIEHS grantee, Dr. Frederick Urbach, and his colleagues at the University of Pennsylvania. This provides heretofore unavailable capabilities for diagnosis of light induced diseases of man, for treatment of certain diseases and for quantitative and qualitative studies of various spectra on tumorigenesis and other photobiologic phenomena.

Skin cancer can now be induced reliably in animals by use of the new equipment and techniques. The techniques also provide predictive capability with respect to the consequences of diminishing atmospheric ozone and the interaction of light and chemicals in photocarcinogenesis of the skin. For example, it was discovered that delayed hypersensitivity plays a protective role in visible light and UV-induced skin cancer. This may be of great significance because it suggests that stimulation of the immune system or other protective mechanisms can prevent or reduce the incidence of skin cancer and that immunotherapy might be of real value.

The existence of melanin pigment protects adequately against skin cancer. People living near the equator or in the southern United States get, at this time, more ultraviolet light than those in the northern part of the United States, and they have a higher incidence of skin cancer. It is calculated that even a small decrease in the ozone layer, such as a 1-percent decrease, may be responsible for a small increase, 1 to 2 percent, in skin cancer in the population.

Because the focus of the ill effect from ozone depletion is mostly on cancer, the NCI is very much involved in this aspect of the problem and will carry on research as part of the total program of the Federal Task Force on Inadvertent Modification of the Stratosphere (IMOS). This is a group of Federal scientists who have coordinated evaluation and assessment of further needs for research on this problem. The NIEHS is represented on this committee.

TRAVEL AND CONFERENCES

Mr. ROYBAL. How much money did you spend on travel and conferences last year?

Dr. RALL. In fiscal year 1975, NIEHS spent approximately $270,000 on travel. Eight conferences were supported in fiscal year 1975 at a total cost of approximately $50,000.

Mr. FLOOD. Mr. Michel?

RESEARCH PRIORITIES

Mr. MICHEL. Have you developed a list of research priorities, and if so, what is it?

Dr. RALL. Yes, Mr. Michel, we have. However, I want to stress that in science, priority settings cannot be a static process, that once accomplished is never modified. Rather it is important, I believe, that we be ready to modify our priorities in the light of new developments and emerging problems. Also at this committee's direction, we have sponsored the second task force on research planning in environmental health science. This task force which is at work now, will be reporting to you next January and undoubtedly its report will cause some adjustments in our priorities.

With that as background our priorities can be summarized as follows:

1. To establish the Institute as a strong coordinating focus for biomedical research in environmental health:
2. To provide a neutral locus for the discussion of environmental health issues;
3. To develop a better understanding of how environmental agents affect man's health;
4. To develop faster, more effective, and less costly methods of environmental agents;
5. To maintain a continuing awareness of what ill effects may result from man's creation of new products and other environmental modifications.

EMPHASIS—DOLLAR STANDPOINT

Mr. MICHEL. What particular area is receiving the most emphasis from a dollar standpoint?

Dr. RALL. Our largest program from a total dollar standpoint is environmental pharmacology and toxicology. In terms of a percentage increase over the 1976 level, the environmental mutagenesis and reproductive toxicology received the most emphasis. As I mentioned earlier, it is estimated that this program will increase by approximately 80 percent over the 1976 level. This is a relatively small program and is of high priority to the Institute.

ENVIRONMENTAL HEALTH SCIENCES CENTERS

Mr. MICHEL. Where are your seven university-based environmental health sciences centers located?

Dr. RALL. The centers are located at Harved School of Public Health; University of Cincinnati College of Medicine; Oregon State University; N.Y. University Medical Center; Vanderbilt University School of Medicine; Mt. Sinai School of Medicine; and the University of Rochester School of Medicine and Dentistry.

HOUSING OF NIOSH PERSONNEL

Mr. MICHEL. As you know, we have appropriated funds to begin planning and construction of a new facility for you in North Carolina. That facility, as I understand it, will be considerably larger than what your immediate needs call for. Would you have any objection to the housing of personnel from the National Institute of Occupational Safety and Health in that facility, perhaps expanding the building somewhat to provide sufficient room?

Would it be easier to work with and coordinate your activities with NIOSH if you were housed in the same facility?

Dr. RALL. The facility we currently have under design and which the Congress has authorized us to construct is significantly smaller than was proposed to the Congress in the early sixties. In addition, we believe that soon after we occupy the building we will need essentially 100 percent of the space.

With regard to the location of NIOSH or any other agency with whom we have close contact, it would be more convenient to have it located nearby. However, the geographical distribution—Washington, Cincinnati, Research Triangle Park—of the agencies we work with is such that this is not possible. Our permanent facilities are to be located on a 509-acre federally owned site in Research Triangle Park. To be located on that site with us is the Health Effects Group of EPA. There is also space available for the location of two additional organizations. I understand, however, that the Secretary has determined that Cincinnati is the most appropriate location for the research laboratories of NIOSH.

RAPID TEST SYSTEM

Mr. MICHEL. In your justification, you state a major obstacle in assessing the mutagenic potential of chemical agents has been the lack of a rapid test system? What do you mean by a rapid test system? How will it be used? When perfected, how many additional agents will you be able to test per year?

Dr. RALL. Because of the large number of untested chemicals in the environment and because of limitations in our capability to test chemicals in animals, other approaches have been under development for the past 5 to 7 years. These new tests consist of microbes—used as detectors of different types of genetic activity—in combination with newly developed techniques for metabolic activation. The microbes are sensitive detectors of damage which would produce gene mutations, chromosome aberrations, or repair of damage to DNA. The in vitro

techniques for metabolic activation make it possible not only to test the original chemical but also derivatives produced as a result of mammalian metabolism.

A battery of indicator organisms will be used to assay and confirm the ability to produce a wide variety of genetic activity.

Compounds giving positive tests will be singled out as possessing potential mutagenic and carcinogenic activity in man. To evaluate this potential, testing will then proceed in high laboratory organisms to collect additional data required for benefit-risk analysis.

An exploratory contract study by NIEHS will evaluate at least 100 compounds per year; an immediate expansion of this contract work could bring the total close to 1,000 compounds per year.

When the rapid test system is perfected and the most ideal indicator organism and test conditions have been selected for routine analysis and mass screening programs and when the computer programs for data storage and analysis have been perfected, we will be limited only by resources with regard to the number of agents which can be tested per year. For example, if the cost per compound is reduced to about $2,500 per compound in the "pilot plant stage" of development, a $6.2 million dollar contract in a single testing laboratory program would permit test of 2,500 chemicals per year. There are at least 3 to 5 laboratories which have or will have such a testing capability in the near future.

ALLOCATION OF NEW RESEARCH GRANTS

Mr. MICHEL. I noticed in your justifications an increase of about $5.6 million for 72 new research grants. How do you plan to allocate these grants among your programs.

Dr. RALL. Eight totaling $598,000 are estimated for environmental mutagenesis and reproductive toxicology; 25 totaling $1,990,000 for etiology of environmental diseases and disorders; 29 totaling $2,252,000 for environmental pharmacology and toxicology; and 10 totaling $738,000 for environmental pathogenesis.

AVERAGE GRANT

Mr. MICHEL. What is your average size grant for this year and the estimate for 1977? How does this compare with previous years? What accounts for the difference, if any?

Dr. RALL. The average size regular research grant for fiscal year 1976 is $81,100 and the estimate for fiscal year 1977 is $87,150, as compared to $66,775 in fiscal year 1975.

Fiscal year 1976 reflects the impact of several awards with a high average cost which were not funded in fiscal year 1975. The difference between fiscal year 1976 and fiscal year 1977 represents an estimated increase of both direct and indirect cost of supporting research. When dealing with relatively small numbers of grants, annual average comparisons are difficult because of the disproportionate impact of relatively few large grants on the average dollar calculation.

Mr. FLOOD. Mr. Conte?

GRANTS

Mr. CONTE. What is your average grant award this year? How does it compare with last year?

Dr. RALL. The average regular research grant award for fiscal year 1976 is $81,100 as compared to $66,775 in fiscal year 1975.

Mr. CONTE. How many approved but unfunded grants will you have this year?

Dr. RALL. The estimated range of approved but unfunded regular research grants in fiscal year 1976 is between 105–115.

DECREASE IN POSITIONS

Mr. CONTE. Why is there a decrease of 33 positions as is shown on page 148 of the justification?

Dr. RALL. The decrease of 33 positions reflected in the budget is due to the fact that the 1977 budget estimate was prepared using a different base than the 1976 appropriated level.

Mr. CONTE. What types of positions are they?

Dr. RALL. The 33 positions are primarily all intramural personnel. The positions are primarily being utilized to initiate new programs in epidemiology and behavioral toxicology, as well as expanson of programs in mutagenesis, teratogenesis, and pharmacology.

NEW CENTER IN 1975

Mr. CONTE. Last year you were in the process of adding a new university-based research center. What is the status of this center?

Dr. RALL. A new center was added in fiscal year 1975 at the University of Rochester School of Medicine and Dentistry, directed by Dr. Thomas Clarkson. This center fills an important gap in studying diseases associated with mercury and other heavy metals in the environment.

FUTURE INCREASE—INTRAMURAL

Mr. CONTE. Do you foresee an increase in your intramural program in coming years?

Dr. RALL. Yes. Now that funds have been appropriated by Congress to begin construction of our permanent facility, NIEHS will move forward with its plans for expansion of the intramural research program.

GRANT SCREENING STAFF

Mr. CONTE. Do you feel that the grant screening staff of your Institute is sufficient?

Dr. RALL. Two additional positions over the fiscal year 1975 level are being added in fiscal year 1976 in the review and approval of grants area. This should provide an adequate level in terms of the current budget.

KEPONE

Mr. CONTE. There has been a great deal in the papers about the pesticide Kepone. Has your Institute done any work on this possible hazard?

Dr. RALL. We are very concerned about Kepone and its effect on those workers exposed in Hopewell, Va.

Early this calendar year we awarded a research contract to the Medical College of Virginia at Richmond to study these victims of Kepone poisoning.

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We hope to understand better the mechanism of toxicity of Kepone and attempt to develop methods either for speeding the elimination of this toxic pesticide from the body or for treating the poisoning.

COORDINATION WITH AGING INSTITUTE

Mr. CONTE. Are you coordinating work with the Aging Institute on environmental factors and diseases associated with aging?

Dr. RALL. We are most interested in developing close and effective coordination with this newly created Institute. As you know the Director has not yet come on board. I plan to meet with him soon after he is on board and develop the basis for an effective relationship.

NITRITES

Mr. CONTE. Do you feel that nitrites used as food preservatives present a danger to consumers?

Dr. RALL. Nitrites as food preservatives definitely represent a dangers to consumers. This is not so much on the basis that nitrites can act as poisons when present in high concentrations, but rather that under certain conditions they may give rise to nitrosamines in food which may increase the load of carcinogens in our population.

There are studies underway to determine under what conditions nitrosamines might not be formed from nitrites and amines, and it may possibly be resolved in the near future. However, at this time nitrites must be considered a health hazard. If the nitrites were removed from certain foods, the older health hazards like botulism may crop up again which would be far more disastrous than the new hazard, but an attempt must be made to find a solution which does not trade one health hazard for another. It may mean much more research by the food industry and more cumbersome controls if nitrites must be maintained at a lower level or cessation of the use of that food for the time being if nitrites are to be completely eliminated.

Mr. FLOOD. Thank you very much.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Amounts Available for Obligation

	1976	1977
Appropriation	$35,915,000	$46,141,000
Pending request	1,745,000	---
Subtotal, Adjusted Appropriation	37,660,000	46,141,000
Comparative transfer from:		
"Office of Director, NIH" (To transfer Standard Level User charge to NIH Management Fund)	120,000	---
Total obligations	37,780,000	46,141,000

National Institute of Environmental Health Sciences

Budget Mechanisms

	1976			1977		
	Number	FTE	Amount	Number	FTE	Amount
Grants						
Regular						
Noncompeting	153	---	$11,847,000	92	---	$9,365,000
Competing	14	---	1,480,000	42	---	2,720,000
New	1	---	130,000	72	---	5,578,000
Supplemental	(1)	---	170,000	(30)	---	290,000
Subtotal	168	---	13,627,000	206	---	17,953,000
Special						
Environmental health sciences centers	7	---	5,287,000	8	---	7,210,000
Research career program	9	---	212,000	19	---	423,000
Scientific evaluation	---	---	37,000	---	---	49,000
Subtotal	16	---	5,536,000	27	---	7,682,000
Total Grants	184	---	19,163,000	233	---	25,635,000
Fellowships						
Noncompeting	20	20	292,000	15	82	1,038,000
Competing	---	---	---	---	---	---
New	---	---	---	41	41	580,000
Supplemental	---	---	---	---	---	---
Subtotal	20	20	292,000	56	123	1,618,000
Training Grants						
Noncompeting	10	112	1,453,000	4	43	625,000
Competing	---	---	---	---	---	---
New	---	---	---	---	---	---
Supplemental	---	---	---	---	---	---
Subtotal	10	112	1,453,000	4	43	625,000
Intramural and direct operations			13,221,000			12,785,000
Standard Level User Charge			120,000			154,000
Research and development contracts			3,211,000			5,000,000
Program management			320,000			324,000
Total			37,780,000			46,141,000

DHEW - National Institutes of Health

CROSSWALK - 1976 COLUMN 1977 JUSTIFICATION

INSTITUTE: National Institute of Environmental Health Sciences
(Dollars in thousands)

Program \ Mechanisms	Research Grants				Training Programs		Intramural and Direct Operations	Research and Development Contracts	Program Management	TOTAL
	Regular Program		Specials							
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Environmental health sciences centers....	---	---	$5,287	---	---	---	---	---	---	$5,287
2. Environmental mutagenesis and reproductive toxicology..	$1,386	$133	---	---	---	$25	---	$716	---	2,260
3. Etiology of environmental diseases and disorders.....	4,146	895	---	$47	$162	122	---	938	---	6,310
4. Environmental pharmacology and toxicology.....	5,415	443	---	202	1,034	145	---	1,496	---	8,735
5. Environmental pathogenesis.....	900	309	---	---	257	---	---	61	---	1,527
6. Intramural and direct operations.....	---	---	---	---	---	---	$13,341	---	---	13,341
7. Program management....	---	---	---	---	---	---	---	---	$320	320
Total obligations...	11,847	1,780	5,287	249	1,453	292	$13,341	3,211	320	37,780

DHEW - National Institutes of Health

CROSSWALK - 1977 COLUMN 1977 JUSTIFICATION

INSTITUTE: National Institute of Environmental Health Sciences
(Dollars in thousands)

Mechanism / Program	Research Grants				Training Programs		Intramural and Direct Operations	Research and Development Contracts	Program Management	TOTAL
	Regular Program		Specials							
	Noncompeting	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships				
1. Environmental health sciences centers....	---	---	$7,210	---	---	---	---	---	---	$7,210
2. Environmental mutagenesis and reproductive toxicology..	$774	$1,288	---	$40	---	$90	---	$1,888	---	4,080
3. Etiology of environmental diseases and disorders.....	4,075	2,565	---	105	$113	431	---	1,136	---	8,425
4. Environmental pharmcology and toxicology.....	3,616	3,577	---	282	512	915	---	1,698	---	10,900
5. Environmental pathogenesis.....	900	---	---	[illegible]	---	[illegible]	---	278	---	[illegible]
6. Intramural and direct operations.....	---		---	---	---	---	$12,939	---	---	12,939
7. Program management....	---	---	---	---	---	---	---	---	$324	324
Total obligations...	9,365	[illegible]	7,210	472	625	1,[illegible]	12,939	5,000	324	46,141

Summary of Changes

1976 Estimated Obligations	$37,780,000
1977 Estimated Obligations	46,141,000
Net change	+8,361,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1976 pay increase	---	$202,000	---	+$69,000
2. Within-grade pay increases	---	40,000	---	+40,000
3. BEC rate increase	---	8,000	---	+2,000
4. Postage increase	---	11,000	---	+2,000
5. Utility increase	---	444,000	---	+90,000
6. General expense and program evaluation	---	376,000	---	+250,000
7. Standard level user charge	---	120,000	---	+34,000
8. Payment to NIH Management Fund	---	772,000	---	+97,000
Subtotal	---	---	---	+584,000
B. Program:				
1. Research grants:				
a. Regular program:				
(1) Noncompeting continuations converted from competing status	---	11,847,000	---	+1,554,000
(2) Competing (new, renewals and supplementals)	---	1,780,000	---	+8,588,000
b. Special programs:				
(1) Environmental health sciences centers	---	5,287,000	---	+1,923,000
(2) Research career programs	---	212,000	---	+211,000
(3) Scientific evaluation grants	---	37,000	---	+12,000
2. Training programs:				
a. Fellowships:				
(1) Noncompeting continuations	---	292,000	---	+919,000
(2) Competing fellowship	---	---	---	+580,000
3. Research and development contracts (new contracts and continuation of ongoing contracts)	---	3,211,000	---	+1,789,000
Subtotal	---	---	---	+15,576,000
Total increases	---	---	---	+16,160,000
Decreases:				
A. Built-in:				
1. One less day of pay in 1977	---	5,035,000	---	-19,000

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
B. Program:				
1. Research grants:				
a. Regular program:				
(1) Noncompeting completed or converted to competing status..	---	11,847,000	---	-4,036,000
(2) Competing completed or converted to noncompeting.....	---	1,780,000	---	-1,780,000
2. Training programs:				
a. Fellowships:				
(1) Noncompeting completed	---	292,000	---	-173,000
b. Training:				
(1) Noncompeting completed	---	1,453,000	---	-828,000
3. Intramural and direct operations	261	12,449,000	-33	-963,000
Subtotal.....	---	---	-33	-7,780,000
Total decreases.....	---	---	-33	-7,799,000
Total net change.....	---	---	-33	+8,361,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Pos.	1976 Revised President's Budget Amount	1976 Appropriation Pos.	1976 Appropriation Amount	1977 Estimate Pos.	1977 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
150	Environmental health sciences centers.....	---	$5,287,000	---	$5,287,000	---	$7,210,000	---	+$1,923,000
151	Environmental mutagenesis and reproductive toxicology.....	---	2,065,000	---	2,260,000	---	4,080,000	---	+1,820,000
153	Etiology of environmental diseases and disorders.....	---	5,195,000	---	6,310,000	---	8,425,000	---	+2,115,000
155	Environmental pharmacology and toxicology....	---	8,140,000	---	8,735,000	---	10,900,000	---	+2,165,000
157	Environmental pathogenesis..	---	1,165,000	---	1,527,000	---	2,263,000	---	+736,000
159	Intramural and direct operations....	228	11,851,000	261	13,221,000	228	12,785,000	-33	-436,000
	Standard Level User Charge...	---	120,000	---	120,000	---	154,000	---	+34,000
161	Program management....	10	320,000	10	320,000	10	324,000	---	+4,000
	Total obligations...	238	34,143,000	271	37,780,000	238	46,141,000	-33	+8,361,000

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	271	238	-33
Full-time equivalent of all other positions	111	111	0
Average number of all employees	362	360	-2
Personnel Compensation:			
Permanent positions	$4,092,000	$4,143,000	+$51,000
Positions other than permanent	1,052,000	1,070,000	+18,000
Other personnel compensation	150,000	160,000	+10,000
Subtotal, personnel compensation	5,294.000	5,373,000	+79,000
Personnel benefits	580,000	588,000	+8,000
Travel and transportation of persons	465,000	450,000	-15,000
Transportation of things	100,000	90,000	-10,000
Rent, communications and utilities	1,145,000	1,235,000	+90,000
Printing and reproduction	90,000	90,000	0
Other Services	2,295,000	2,014,000	-281,000
Project contracts	3,211,000	5,000,000	+1,789,000
Payment of the NIH Management Fund	892,000	1,023,000	+131,000
Supplies and materials	2,000,000	1,800,000	-200,000
Equipment	800,000	600,000	-200,000
Grant, subsidies and contributions	20,908,000	27,878,000	+6,970,000
Total obligations by object	37,780,000	46,141,000	+8,361,000

Significant Items in House and Senate
Appropriation Committee Reports

Item	Action taken or to be taken
1976 House Report	
1. The Committee believes it is appropriate that the NIEHS develop a new Task Force to identify, review and evaluate the needs in this area. In view of the broad sweeping nature of the task, and the time necessary to accomplish the original study, the Committee believes that two years will be required for this study and directs the Institute to report to it in January 1977. The Committee directs the Institute also to charge the Task Force with responsibility for identifying specialized manpower requirements in this area. (page 43)	1. The Second Task Force on Research Planning in Environmental Health has been established and its organizational meetings were held in December, 1975. Planning meetings will be held throughout the Spring of 1976 culminating in a major working meeting in June. The report will be submitted to the committee in January, 1977.
2. The Committee is including an additional one million dollars to permit continued funding of the studies of the effects of orally ingested asbestos. (page 44)	2. The additional one million dollars will enable NIEHS to continue the two research contracts awarded in 1975. These contracts will conduct life-time studies of the effects of ingested asbestos in experimental animals.
3. Because of its importance as a focal point for environmental health research and its resulting need to be heavily engaged in interagency cooperation and collaboration, the NIEHS is particularly dependent upon the continued growth and vitality of its intramural program. To strengthen this vital activity the Committee directs that 1.5 million of the increase over the budget estimate be used for the intramural research program, including the requisite additional personnel. (page 45)	3. The increase of $1.5 million and 33 additional positions for 1976 will enable NIEHS to develop new programs in behavioral toxicology and epidemiology as well as further develop its programs in environmental mutagenesis, teratogenesis, marine biomedicine, and pharmacology.
4. The Committee has included $64 million in the NIH Buildings and Facilities appropriation for the construction of a research facility at Research Triangle Park, North Carolina. (page 45)	4. Funds in the amount of $25 million agreed to in Conference have been included in the 1976 Buildings and Facilities Appropriation.
1976 Senate Report	
1. The Committee is concerned that because of inadequate resources the independent marine laboratories may be forced to close in the coming years. Accordingly, the Committee directs the NIEHS to develop a program of core support for operating those marine laboratories whose programs offer the best opportunities for advancement of marine biomedical research. (page 61)	1. The Institute is currently engaged in planning activities to determine the needs of the nation's marine laboratories. The Institute plans to propose a program in this area for Fiscal Year 1978.

Authorizing Legislation

Legislation	1977 Authorization	1977 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	$43,898,000 2/
Title IV, Part I--National Research Service Awards	1/	2,243,000 2/

1/ Authorization expired June 30, 1975, extension legislation is pending.

2/ Funding estimate only.

National Institute of Environmental Health Sciences

Year	Budget Estimate to Congress	Comparable House Allowance	Comparable Senate Allowance	Appropriation
1967	$24,432,000	$24,418,000	$24,418,000	$24,418,000
1968	20,016,000	16,690,000	20,016,000	16,690,000
1969	17,668,000	17,110,000	17,668,000	17,389,000
1970	17,897,000	17,897,000	17,897,000	17,897,000
1971	19,517,000	20,187,000	21,187,000	20,187,000
1972	24,960,000	26,065,000	31,565,000	26,065,000
1973	28,652,000	30,532,000	31,576,000	30,532,000*
1974	25,383,000	28,999,000	28,999,000	28,517,000**
1975	28,804,000	32,714,000***	35,069,000	35,057,000*
1976	31,233,000	37,780,000	37,780,000	
Items pending		(1,745,000)	(1,745,000)	
1977	46,141,000			

*Appropriation after reduction as authorized by P.L. 93-192.

**Appropriation after reduction.

***Excludes Research and Development Contracts not considered by the House due to lack of authorization.

"The figures presented in this table have been adjusted to reflect the transfer of major functions. This presents a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of General Research Support Grants is no longer the function of this Institute. The amount originally contained in this account in previous years for this particular program has been removed for comparability purposes".

National Institute of Environmental Health Sciences

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	37,660,000	37,660,000	
Items pending		(1,745,000)	(1,745,000)	
1977	46,141,000			

*Appropriation after reduction as authorized by P.L. 93-192.

**Appropriation after reduction.

***Excludes Research and Development Contracts not considered by the House due to lack of authorization.

Justification

National Institute of Environmental Health Sciences

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Environmental health sciences centers..	---	$5,287,000	---	$5,287,000	---	$7,210,000	---	+$1,923,000
Environmental mutagenesis and reproductive toxicology	---	2,065,000	---	2,260,000	---	4,080,000	---	+1,820,000
Etiology of environmental diseases and disorders.....	---	5,195,000	---	6,310,000	---	8,425,000	---	+2,115,000
Environmental pharmacology and toxicology.....	---	8,140,000	---	8,735,000	---	10,900,000	---	+2,165,000
Environmental pathogenesis.....	---	1,165,000	---	1,527,000	---	2,263,000	---	+736,000
Intramural and direct operations.	228	11,971,000	261	13,341,000	228	12,939,000	-33	-402,000
Program management..	10	320,000	10	320,000	10	324,000	0	+4,000
Total.....	238	34,143,000	271	37,780,000	238	46,141,000	-33	+8,361,000

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. This is based on two premises: (1) environmental agents can cause disability, disease, and death; and (2) results from biomedical research can be used to prevent or ameliorate environmental diseases and disorders. 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 concentration 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 for 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. 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 Intramural program gives priority to research areas in which there is an insufficient information base for adequate understanding of environmental hazards or for regulatory decisions. It investigates the actions, interactions, and mechanisms by which chemical, physical and biological agents damage the structure or function of biological systems at any level and, where possible, the effects found in experimental models are compared with effects in man. However, because of the general insufficiency of data for such comparisons, a major effort is being made in comparative physiology and toxicology and in biometrics in order to develop capabilities for reliable extrapolation of data from physical and biological models to man.

The Institute's extramural and intramural programs are a blend of fundamental and applied research in areas identified as justifying broad scale investigation. For administrative purposes the research is circumscribed within six programs: (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 programs serve as a prime and unique focus for National and International efforts to evaluate and ameliorate the negative impact of environmental factors on human health.

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

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Environmental health sciences centers...	7	$5,287,000	7	$5,287,000	8	$7,210,000	+1	+$1,923,000

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 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 1977

The Centers, each in accord with the specialties and research expertise of its staff, make 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. One new center established in late FY 1975 fills an important gap in diseases associated with mercury and other heavy metals in the environment. 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 requested funds will permit the funding of one new multidisciplinary center concerned with the impact of environmental agents with primary emphasis on cardiac and pulmonary physiology, as well as continuation costs of the seven currently active centers.

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Environmental Mutagenesis and Reproductive Toxicology

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research grants:								
Regular:								
Noncompeting...	23	$1,386,000	23	$1,386,000	12	$774,000	-11	-$612,000
Competing.....	1	56,000	2	133,000	18	1,288,000	+16	+1,155,000
Subtotal,....	24	1,442,000	25	1,519,000	30	2,062,000	+5	+543,000
Special.....	---	---	---	---	2	40,000	+2	+40,000
Subtotal, Research grants	24	1,442,000	25	1,519,000	32	2,102,000	+7	+583,000
Fellowships.....	2	25,000	2	25,000	7	90,000	+5	+65,000
Training grants....	---	---	---	---	---	---	---	---
Research and development contracts...	5	598,000	7	716,000	12	1,888,000	+5	+1,172,000
TOTAL.....	31	2,065,000	34	2,260,000	51	4,080,000	+17	+1,820,000

Introduction

The mutagenesis and reproductive toxicology program deals with delineating known and potential roles of chemical agents found in air, water, food and occupational situations, in altering 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 the most profound long-term 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 and extrapolation of results from laboratory test systems to man.

Program Plans for 1977

Advances are being made toward further understanding of the chemistry of molecular interactions between DNA and mutagenic agents such as azides, 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 to develop new procedures. This is a high priority aspect of the program. The Institute recognizes serious deficiencies in available mutagenesis testing procedures; and, in many 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 have been 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, chlorinated furans and dioxins, heavy metals, 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. 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

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research grants:								
Regular:								
Noncompeting..	42	$4,146,000	42	$4,146,000	25	$4,075,000	-17	-$71,000
Competing.....	1	77,000	3	895,000	33	2,565,000	+30	+1,670,000
Subtotal....	43	4,223,000	45	5,041,000	58	6,640,000	+13	+1,599,000
Special.....	2	47,000	2	47,000	5	105,000	+3	+58,000
Subtotal, research grants	45	4,270,000	47	5,088,000	63	6,745,000	+16	+1,657,000
Fellowships.....	8	122,000	8	122,000	16	431,000	+8	+309,000
Training grants...	2	162,000	2	162,000	1	113,000	-1	-49,000
Research and development contracts..	3	641,000	5	938,000	5	1,136,000	0	+198,000
TOTAL.....	58	5,195,000	62	6,310,000	85	8,425,000	+23	+2,115,000

Introduction

The central objective of the etiology program is to identify 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 and energy development in such a way as to make them compatible with human health and well-being.

Program Plans for 1977

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. The potential of certain of these compounds to modify man's behavior is exemplified by recent reports of brain and neural disorders caused by the pesticide kepone. Further probing of the long-term effects of mercury and lead in the central nervous system has verified and extended our knowledge of the 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 will continue to be 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 thiolsulfonates. These compounds circulate in the blood stream, releasing sulfite throughout the body. Hydrazine, used in making a number of useful pharmaceuticals, 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 unrecognized 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 families of workers exposed in their jobs to asbestos, and on the general population in urban areas, because residents of large cities inhale substantial amounts of airborne asbestos and other potentially carcinogenic air pollutants throughout their lives. The same kinds of hazards have now been found to exist in automobile brake repair shops where asbestos particles are disseminated during installation of brake linings.

Further studies will be 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 efforts 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. Work will 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

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research grants:								
Regular:								
Noncompeting.....	78	$5,415,000	78	$5,415,000	45	$3,616,000	-33	-$1,799,000
Competing.....	2	91,000	7	443,000	52	3,877,000	+45	+3,434,000
Subtotal.....	80	5,506,000	85	5,858,000	97	7,493,000	+12	+1,635,000
Special.....	7	202,000	7	202,000	10	282,000	+3	+80,000
Subtotal, Research grants	87	5,708,000	92	6,060,000	107	7,775,000	+15	+1,715,000
Fellowships.....	10	145,000	10	145,000	25	915,000	+15	+770,000
Training grants.....	7	1,034,000	7	1,034,000	3	512,000	-4	-522,000
Research and development contracts.....	5	1,253,000	7	1,496,000	7	1,698,000	0	+202,000
TOTAL.....	109	8,140,000	116	8,735,000	142	10,900,000	+26	+2,165,000

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 1977

Studies are continuing on the nature of those enzymes which 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.

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 methyl-mercury 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.

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.

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.

Plans are to continue two research contracts awarded in 1975 to conduct life-time studies of the effects of ingested asbestos in experimental animals. These contracts were awarded in response to Congress' directive that the Institute initiate a long-term study on the effects of ingested asbestos.

Environmental Pathogenesis

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Budget Mechanism:								
Research grants:								
Regular:								
Noncompeting.....	10	$900,000	10	900,000	10	$900,000	0	0
Competing.....	---	---	3	309,000	11	858,000	+8	$549,000
Subtotal.....	10	900,000	13	1,209,000	21	1,758,000	+8	+549,000
Special.....	---	---	---	---	2	45,000	+2	+45,000
Subtotal, Research grants	10	900,000	13	1,209,000	23	1,803,000	+10	+594,000
Fellowships.....	---	---	---	---	8	182,000	+8	+182,000
Training grants.....	1	257,000	1	257,000	---	---	-1	-257,000
Research and development contracts.....	1	8,000	2	61,000	3	278,000	+1	+217,000
TOTAL.....	12	1,165,000	16	1,527,000	34	2,263,000	+18	+736,000

Introduction

The pathogenesis program focuses upon the details and time sequence of molecular and cellular events that culminate in recognizable diseases and endpoints 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.

Program Plans for 1977

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. These studies have formed the basis for estimations of the adverse human health effects and of depletion of the ozone layer attributed to chlorofluorohydrocarbons. 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 will continue 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. Continuing studies will 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 and Direct Operations

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Intramural laboratory and clinical research	203	$10,714,000	236	$12,084,000	203	$11,368,000	-33	-$716,000
Other direct operations	25	1,257,000	25	1,257,000	25	1,571,000	---	+314,000
Total, intramural and direct operations	228	11,971,000	261	13,341,000	228	12,939,000	-33	-402,000

Introduction

This activity suppports the intramural research program, the review and approval of grants (Office of Extramural Program) and contracts, and the provision of centralized administrative and clerical services. 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 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.

The Office of Extramural Program 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 1977

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 is 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.

The mutagenesis program at NIEHS is the only broad-based program in environmental mutagenesis in the government and, hence, will function centrally in collaboration with governmental and non-governmental agencies. Research is being aimed at the development of faster, more effective methods of testing compounds for their mutagenic potential. These methods are urgently needed to determine the safety of chemicals already in use as well as numerous chemicals being developed for use each year.

An additional objective is to explore the correlation between carcinogenesis and mutagenic activity of environmental chemicals and to get some understanding of this relationship at the molecular level. This information should make it possible to develop short-term tests for mutagenic activity which can predict carcinogenic activity in man. Such a capability would reduce the cost of the standard toxicological evaluation of new chemicals by industry when these short-term tests are performed during the early stages of product development.

Research efforts in the area of marine biomedicine will be intensified. Because these marine species are often important components of the human diet and could serve as sources of toxic human exposures to chemicals, the Institute is studying how marine organisms handle these various agents and their interactions. Another 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.

The Institute will be seeking to develop mechanisms for the selection of environmental chemicals for teratogenicity (birth defects) testing and to establish priorities for testing. The major goal of the NIEHS teratology program is not screening chemicals per se, but trying to improve the screening methods to make them as applicable as possible to man.

Scientists have recently developed a mouse model of the toxic effect of the synthetic estrogen diethylstilbestrol (DES) that may permit investigators to determine how the unborn animal handles DES. DES is currently used as a "morning after" contraceptive and as an animal feed additive to speed up weight gain. This model will be useful for studying factors associated with transplacental carcinogenesis, or cancer produced in offspring of exposed mothers. In addition it hopefully will lead to the development of predictive indicators of cancer which might be applied to the human population.

Scientists are working on developing a program in behavioral toxicology. In many instances behavioral changes occur before significant somatic cell changes can be demonstrated. This program will attempt to define methods of determining how environmental stresses produce behavioral alterations in mammals and lower species.

Plans are being made to initiate a program in epidemiology. Epidemiology plays a vital role in health research. It is the major tool used to identify factors associated with human disease through study of effects in populations exposed to environmental agents in a real life setting. Epidemiological studies may provide the first clue to adverse effects of exposure to an environmental agent, or they may be used to test hypotheses generated by experiments on laboratory animals.

Research is being continued at 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 will be expanded as funds and additional manpower become available.

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 are 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.

Program Management

	1976 Revised President's Budget		1976 Appropriation		1977		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount	Pos.	Amount
Program management..	10	$320,000	10	$320,000	10	$324,000	0	+$4,000

Introduction

This activity supports the Office of the Director 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 of supervision of centralized administrative services.

Program Plans for 1977

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 1977. The Director also serves as Project Chairman of the US-USSR Working Group on the Biology and Genetic Effects of Pollutants. In addition, the Director serves as Chairman of the DHEW Committee to Coordinate Toxicology and Related Programs. Also, the Institute continues to support topical conferences on environmental health problems of immediate interest. Eight of these conferences were supported in 1975 and twelve in 1976. Conferences of this nature will continue to be supported in 1977. These conferences attract scientists from industry, universities, government, and foreign countries. Usually their proceedings are published in the Institute's Journal, Environmental Health Perspectives.

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

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$5,287,000	Indefinite	---	$7,210,000

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 1976. 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 1976: 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 have been 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 has been 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 late in FY 1975.

Objectives for 1977: The budget request provides for funds to continue support of the 7 Centers funded in 1976, and the initiation of 1 new center concerned with the impact of environmental agents on biological systems with primary emphasis on cardiac and pulmonary physiology.

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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$2,260,000	Indefinite	---	$4,080,000

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. Critical is the need 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 also being made to assess existing mutagenesis test procedures for relevance to man and to develop 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 additivies and natural products for mutagenic potential in man.

Accomplishments in 1976: Progress has been 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 have ranged 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 have been 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 1977: The budget request provides for continuation and expansion of 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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$6,310,000	Indefinite	---	$8,425,000

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 1976: 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 has revealed 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, has 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 have been made in understanding the influence of heat stress, light, noise, microwaves and laser radiation on physiological systems. New insights have been 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 have provided 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 1977: The budget request provides for continuation and expansion of 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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$8,735,000	Indefinite	---	$10,900,000

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 1976: The nature of those body enzymes that alter foreign compounds 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. Plans are to continue two research contracts awarded in 1975 to conduct lifetime studies of the effects of ingested asbestos in experimental animals. These contracts were awarded in response to Congress' directive that the Institute initiate a long-term study on the effects of ingested asbestos. A research contract was awarded in 1976 to develop biological information on the chlorinated hydrocarbon pesticides kepone. In addition to being implicated as a case of serious illness in factory employees, kepone may prove to be a cancer-producing agent in exposed employees, relatives and persons living hear the factory.

Objectives for 1977: The budget request provides for continuation and expansion of 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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,527,000	Indefinite	---	$2,263,000

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 1976: 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 1977: 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.

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NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Intramural and Direct Operations
(Public Health Service Act, Title III, Part A)

1976			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
261	$13,341,000	Indefinite	228	$12,939,000

Purpose: This activity support the intramural research program, review and approval of grants (Office of Extramural Program) and contracts, and the provision of centralized administration and clerical services. 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 of sources of such factors.

Explanation: The intramural 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 in administrative and clerical services are provided. The Office of Extramural Program 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.

Accomplishments in 1976: Considerable effort has been devoted to development of basic information regarding the sites and mode of action of heavy metals. Progress has been made toward elucidation of structure activity relations, metabolism, pharmacodynamics, mechanisms of action and mechanisms of detoxication and toxicity enhancement of chlorinated hydrocarbons such as PCBs, furans and dioxins, benzenes, and others. 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 has been 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 have been made in the host mediated assay and other test systems for mutagenicity. Work has been expanded and progress has been 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 have organized and sponsored 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. The Extramural program staff has advanced its efforts to strengthen its liaison and management activities in order to obtain maximum benefits from the available grant funds.

Objectives for 1977: The budget request provides for continuation of the intramural research program at a reduced level from 1976. The Extramural program staff will maintain surveillance over approximately 350 grants during this year.

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

Program Purposes and Accomplishments

Activity: Program Management
(Public Health Service Act, Title III, Part A, Title IV, Part I)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
10	$320,000	Indefinite	10	$324,000

Purpose: This activity supports the Office of the Director 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 supervision of centralized administration and clerical services.

Accomplishments in 1976: During 1976, the Office of the Director has 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 has served as the American Coordinator of the Environmental Health Sciences portion of the US-USSR Health Agreement. Exchange of scientists under this agreement has begun and will continue in 1977. The Director has also served as Project Chairman of the US-USSR Working Group on the Biological and Genetic Effects of Pollutants. In addition, the Director has served as Chairman of the DHEW Committee to Coordinate Toxicology and Related Programs. Also, the Institute has supported 12 conferences in 1976 on environmental health problems of immediate interest.

Objectives for 1977: 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.

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Estimate	Transition Quarter
Environmental health sciences centers	$5,287,000	$2,022,000
Environmental mutagenesis and reproductive toxicology	2,260,000	654,000
Etiology of environmental diseases and disorders	6,310,000	767,000
Environmental pharmacology and toxicology	8,735,000	628,000
Environmental pathogenesis	1,527,000	424,000
Intramural and direct operations	13,341,000	3,212,000
Program management	320,000	83,000
Total obligations	37,780,000	7,790,000

The estimate for the three-month period reflects a continuation of the programs of the National Institute of Environmental Health Sciences. These amounts are consistent with the 1976 President's Budget and accounting data for the first quarter of FY 1975.

RESEARCH RESOURCES

WITNESSES

DR. THOMAS G. BOWERY, DIRECTOR
DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. ROBERT W. LAMONT-HAVERS, DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH
DR. JAMES F. O'DONNELL, ASSISTANT DIRECTOR, DIVISION OF RESEARCH RESOURCES
RICHARD L. SHAFER, EXECUTIVE OFFICER, DIVISION OF RESEARCH RESOURCES
BERTIL G. BERGQUIST, BUDGET OFFICER, DIVISION OF RESEARCH RESOURCES
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. FLOOD. We have now "Research Resources."

For "Research Resources" the presentation will be made by Dr. Thomas G. Bowery, the Director.

We have a biographical sketch of you which we will place in the record at this point.

[Dr. Bowery's biographical sketch follows:]

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, 1968–1969. Associate Director for Operations, Division of Research Facilities and Resources, National Institutes of Health, 1967–1968. Assistant Chief for Operations, Division of Research Facilities and Resources, NIH, 1965–1967. Extramural Operation, and Procedures Office, Office of the Director, NIH, 1964–1965. Special Assistant to th Associate Director for Research Grants, Office of the Director, NIH, 1963–1964. Grants Associate, Division of Research Grants, NIH, 1962–63. Research professor, department of entomology, North Carolina State College, Raleigh, N.C. 1959–1962. Research associate professor, department of chemistry, North Carolina State College, Raleigh, N.C., 1953–1959. Research assistant professor, Pesticide Residue Laboratory, Everglades Experiment Station. University of Florida, Belle Glade, Fla., 1951–1952. Research associate in chemistry, office of the State chemist, New Jersey Agricultural Experiment Station New Brunswick, N.J., 1948–1951. Research fellow, entomology department, Rutgers University, New Brunswick, N.J., 1946–1948.
Association membership: American Association for the Advancement of Science, American Chemical Society, and Sigma Xi.
Publications: Author of some 23 publications in 7 journals.

Mr. FLOOD. You have people here.

Dr. BOWERY. Yes, sir. On my far left is Mr. Bergquist, who has been before the committee several times. On my near left is Richard L. Shafer, Executive Officer of the Division, having moved up from his former position as Administrative Officer.

Mr. FLOOD. You have a statement. How do you want to handle it?

Dr. BOWERY. I would like to insert the full statement in the record and verbally offer a short summary statement that runs about 2½ minutes.

Mr. FLOOD. Fine.

[The statement follows:]

It is a pleasure to appear before you again on behalf of the Division of Research Resources to discuss our budget request for 1977. As was true in years past, the success of the Nation's health and biomedical research depends strongly on the provision of sufficient high-quality research resources. This Division's mission is to assure the availability of resources, such as laboratory animals and primates, clinical research environments, and technology and its applications for biomedical research. It is also our mission to determine the needs and opportunities occurring nationwide in biomedical research and to be aware of areas in which our resources can be brought to bear on the critical research activities. One of the ways we can accomplish our mission is to continually meet with other officials of the NIH and with representatives of grantee institutions across the country, assessing their needs and, simultaneously, informing them of developments in technologies, clinical techniques, and the animal models and other resource apportunities which we are providing. Last year, over 5,000 NIH-funded research projects used at least 1 DRR-supported resource.

MINORITY BIOMEDICAL SUPPORT

A new source of qualified investigators in the biomedical research field is last year's participants in our minority biomedical support program. Faculty, graduate and undergraduate students together completed work on many research projects and presented over 350 papers depicting their research results. Of this population, 293 undergraduate students finished their undergraduate training and 225, or 75 percent of these graduates, were admitted to medical, dental, and other health-related schools or to graduate schools. We believe this is a significant accomplishment in the minority program and we expect this kind of output to continue. In the coming year, we anticipate the minority biomedical support program supporting 75 grants at 80 minority institutions with as many as 1,900 individuals participating in the research projects supported by these grants. Prior to the initiation of this program in 1972, the minority community was a largely untapped "human resource" as participants in biomedical research. The program improves the access of minority faculty and students to opportunities for participation in biomedical research careers.

BIOTECHNOLOGY RESEARCH

Nearly 1,000 NIH-supported research projects took advantage of the technological capabilities at our 47 biotechnology research resources last year. These projects represent approximately $64,000,000 of NIH categorical Institutes' extramural support. Because the biotechnology resources are expensive, high-quality centers, we have encouraged that these centers be used, not only by investigators who work where our resources are located, but by investigators located elsewhere. During 1975, about one-quarter of the investigators sharing these resources came from institutions outside the grantee center. We plan to extend the concept of resource-sharing as much, and as far, as possible in the coming year. Scientific applications of our biotechnology research program involve such projects as developing a computer-based consultation system for diseases of the eye, modeling the decision processes which medical experts go through in determining which therapy to use for patients with bacterial infections, and assisting biochemists in understanding normal and abnormal cell structures. In a cooperative effort with our general clinical research centers program, investigators are designing a computer-based research data management system for use by clinical investigators. This system will be helpful to the researcher in analyzing clinical research data results and, in fact, extend the

ability of the researcher both by saving time and by providing new insights into the meaning of the data discovered. Other technologies supported by this program enable researchers to learn more about the dynamic structure and function of tissues, organs and other biological material and the actions of diseases on these structures so that corrections for disease defects may be discovered.

CHEMICAL/BIOLOGICAL INFORMATION HANDLING RESEARCH

The chemical/biological information handling research program is also engaged in applying technology to the needs of biomedical research. This contract-based program has, as its specific aim, to develop new computer-based tools for handling research information about chemical substances and their biological effects. The heart of this program and our efforts is a comprehensive array of computer tools called Prophet. Scientists use Prophet to acquire more basic biological and chemical knowledge at the molecular and submolecular level. This knowledge can reduce the time and costs associated with the development of new drugs and, thereby, improve the level of health care in this country. Currently, over 100 investigators use Prophet in 12 geographic areas.

LABORATORY ANIMAL SCIENCE AND PRIMATE RESEARCH

Our seven Primate Research Centers are currently supporting 152 staff scientists. In addition, the Primate Research Center facilities are shared with 432 collaborative scientists from numerous universities. Studies currently underway in the Primate Centers include those on social and behavioral effects of malnutrition, the effects of environmental pollutants on respiratory function, metabolic bone disease studies, and investigations on language-learning processes and related behaviors.

It is important to remind you again that the national problem of obtaining sufficient nonhuman primates for research purposes is a critical one. The Centers are now producing approximately 50 percent of their own primate requirements. Also, we will support eight domestic primate breeding colonies which will eventually supply approximately 20 percent of the requirements of the NIH-supported extramural investigators who now do their work outside the Primate Research Centers.

We are now engaged with NIH's Division of Research Services, other PHS agencies, the National Science Foundation, and the Department of Defense in the Inter-Agency Primate Steering Committee. This committee is coordinating the solution to the problem of the critical shortage of nonhuman primates for research use.

Our diagnostic and investigative laboratories exist to improve the health of animals in the research colonies. These laboratories contribute to the quality of about 885 NIH-supported research projects which are funded at nearly $56 million.

Since 1971, the Division of Research Resources has awarded grants to institutions to improve their facilities for animals which are used in over 1,400 research projects, currently funded at $90 million. We are also supporting about 20 projects to define, characterize, or exploit the naturally occurring biological attributes of certain animals' usefulness in biomedical research. For example, one of our projects showed that nonhuman primates develop humanlike irregularities or stoppages of the normal breathing impulses. In 1977, our seven Primate Research Centers and 82 laboratory animal research projects will provide support of facilities, animals, and technical expertise and advice to over 2,600 NIH-supported extramural research projects.

CLINICAL RESEARCH

Many advances in clinical research come to fruition only after extensive and controlled research protocols have been carried out in clinical settings. It is for this reason that we support 785 clinical research beds in our General Clinical Research Centers program. These beds are located in 84 centers around the Nation in teaching hospitals of medical schools. Among the costs that we fund are salaries of nearly 1,700 full-time, research-trained physicians, nurses, dieticians, technicians, and social workers. This program is important to NIH-funded extramural research because it supports more than 75 percent of all the dedicated, extramural research beds funded by NIH. Patient-oriented investigations in these centers

cover the medical research spectrum from cancer therapy, organ transplantation, obesity, diabetes, disorders of growth, heart disease, high blood pressure, mental retardation and others. The more than 1,500 investigators who use the General Clinical Research Centers are supported by grants and contracts from NIH categorical Institutes programs, funded at approximately $280 million. Healthy patients plus patients who have chronic diseases but do not require hospitalization, and ill patients who do need to be hospitalized are involved in research utilizing the clinical centers. For both ill and healthy patients, the program supports only the costs associated with research. With the funds requested, we plan to support 83 centers in fiscal 1977, and provide staff and facilities to see 205,000 inpatients and 75,000 outpatients for research purposes. As testimony to the value and quality of the General Clinical Research Centers program, we note, with pride, the recommendation of the National Commission on Diabetes, from volume I of the reports to the Congress.

THE LONG-RANGE PLAN TO COMBAT DIABETES

"Clinical research can most effectively incorporate the successful results of basic research through increased support for the existing General Clinical Research Centers."

BIOMEDICAL RESEARCH SUPPORT

The narrative justification before you requests no funds for the biomedical research support grant program in fiscal year 1977. This is based on the assessment that the objectives of the program had been attained and that the research needs of the Nation could better be served by the continued substantial support of the regular categorical research grant effort.

DISSEMINATION OF INFORMATION

Our grantees are encouraged to disseminate information to both professional and public groups. For example in July 1975, a group of 26 science writers and 7 television crews heard the latest results from our Primate Research Center at Davis, Calif. The stories concerned the effects of birth defects in monkeys and their implications for humans; and the effects of marihuana. This concentrated news gathering produced over 100 newspaper and magazine articles throughout the United States. Also, the Division sent out a total of 22,000 publications and, in addition, handled 5,400 requests for information and assistance for locating desired information.

With regard to distributing information to other professionals throughout the United States, the Simian Virus Reference Laboratory in San Antonio, Tex., provided information regarding the immune status of subhuman primates and the possible cause of outbreaks of overt diseases. Over 48 laboratories submitted nearly 2,400 specimens for antibody surveys or virus isolation and identification. The Registry of Comparative Pathology has continued to augment its collection of specimens from primates and other laboratory animals, domestic and wild animals, fish and birds leading to a specialized course in comparative pathology utilizing the new findings. This course was offered to professionals this past May. In addition, the primate research program publishes its own laboratory primate newsletter which has a mailing list of 1,700 individuals and organizations. The newsletter provides information on maintenance, breeding, and procurement of nonhuman primates for laboratory studies. In addition to our primary information dissemination efforts, research resources carry within themselves a natural information sharing function. For example, resource sharing activities tell both potential and actual users of the technology that is available and how it could apply to their research.

The Division of Research Resources' staff assembles scientists to encourage the interchange of ideas about resource improvement and utilization. About six workshops are planned for next year covering such subjects as the application of artificial intelligence to biomedical research, computer graphics application to biological structure and the use of higher atomic resolution so that cell structure can be viewed faster, cheaper, and more accurately than by existing methods. Finally, well over 5,000 books, scientific papers, and journal articles were published last year, reporting results obtained from research using the Division's resources.

FUTURE PLANS AND BUDGET

In the next year, we will be continuing support of our research resources to assure their availability to investigators throughout the Nation. But, within each resource, we are continually looking for improvements, new technological applications, new animal models, new breeding and quality control techniques, new clinical research procedures, and new ways to cut ever-rising costs.

In conclusion, Mr. Chairman, the budget request for the Division of Research Resources for 1977 is $92,342,000. I shall be pleased to answer any questions and supply additional information which you desire for the record.

Dr. BOWERY. The provision and management of research resources play a vital and continuing role in the conduct of health and biomedical research. For example, the General Clinical Research Centers currently support 785 beds in 84 clinical research centers and a staff of nearly 1,700 research-trained personnel which provides for 75 percent of NIH's extramural research bed capacity. The biotechnology resources program provides unique technological support for almost 1,000 NIH research projects. For example, nearly 1,500 investigators used 16 computer research facilities last year to do research on some 600 projects. The minority biomedical support program provides a mechanism for all NIH institutes to pursue their interest in support of biomedical research by over 1,900 minority persons. The laboratory animal sciences program supports animal facility improvement projects and diagnostic laboratories which improve the quality of animals used in over 2,500 NIH-supported research projects. The primate research centers program provides resources utilized by over 900 biomedical investigators supported by NIH. All together, over 5,000 research projects used one or more of our research resources last year. In other words, research investigators funded for $500 million by the categorical institutes of NIH, used DRR's resources to help accomplish their objectives.

Thus, the Division's mission is to assure the availability of resources, such as laboratory animals and primates, clinical research environments. and technology and its applications for biomedical research. It is also our mission to sense the needs and opportunities occurring nationwide in biomedical research and to be aware of areas in which our resources can be brought to bear on the critical research activities. One of the ways we accomplish our mission is to continually meet with other officials of the NIH and with representatives of grantee institutions across the country, assessing their needs and simultaneously informing them of developments in technologies, clinical techniques, and the animal models and other resource opportunities which we are providing. The Division also cooperates with other Government agencies to solve urgent research resource problems. As an example, we are now engaged with NIH's intramural Division of Research Services, other PHS agencies, the National Science Foundation, and the Department of Defense in the Inter-Agency Primate Steering Committee. This committee is coordinating the solution of the problem of the critical shortage of nonhuman primates for research use.

Mr. Chairman, our budget request for the Division of Research Resources for 1977 is $92,342,000. I will be pleased to answer any questions and to supply additional information which you desire for the record.

Mr. FLOOD. Doctor, here we go again on the merry-go-round. We have been at this three or four times, as you know. I see again you are proposing to eliminate the biomedical research support grant program that was formerly called general research support program.

Dr. BOWERY. That is correct.

Mr. FLOOD. Do you want to state once again why this program is no longer needed?

Dr. BOWERY. There are at least three sets of perspectives involved here: First, when one works with the advisory apparatus and with the grantee institutions involved you still feel that the program is valuable, useful, and unique; second, when one is forced to reduce or offset within the constraints of a given budgetary framework, you tend to place this program in a lower order of priority; third——

Mr. FLOOD. You want to realine the priorities. That is the magic phrase?

Dr. BOWERY. I felt if I would have to take $42 million out of the Division's clinical research centers, animal resources, minority biomedical support, or biotechnology resources it would be inappropriate to do so.

Mr. FLOOD. Can you give us some examples of the kind of research that will be supported by this program in fiscal 1976? If you can't for 1976, give them to us for 1975.

Dr. BOWERY. There is a vast array of all types of biomedical research that takes place in this program.

Mr. FLOOD. Just give us some examples for 1976.

Dr. BOWERY. I think a good example is some of the early pioneering work on the use of certain bile acids to dissolve gallstones first carried out by a young investigator using biomedical research support funds. Dr. J. L. Thistle, a new young investigator at the Mayo Clinic in Rochester, Minn., received $10,000 of biomedical research support funds to initiate studies on the effects of chenic acid in the dissolution of gallstones.

Mr. FLOOD. Is that different from the British proposal?

Dr. BOWERY. I am not familiar with that. I am familiar with the work now supported by the Arthritis Institute.

Mr. FLOOD. You are not aware of the British proposal?

Dr. BOWERY. I am sure much of this work started in the United States and was fostered through the Division's biomedical research support program and the general clinical research center's program. Some of that pilot work led to a controlled clinical trial under the leadership of Dr. Alan F. Hofmann at the Mayo Clinic in Rochester, Minn. The controlled clinical trial, utilizing chenic acid dosage, was conducted with 30 men and 26 women at the Mayo General Clinical Research Center which is supported by NIH's Division of Research Resources. After 6 months, more than half the patients showed reduction in gallstone size. Subsequent X-rays revealed the gallstones had disappeared in 13 of the patients. Subsequently, the concept of cholesterol gallstone dissolution by oral dosage of chenic acid is being evaluated, with controlled toxicity studies, in a national cooperative trial funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases by gallstones study centers throughout the country. Approximately 100 patients will be treated in each center. That is one example of how the flexibility of the biomedical research support

program paid off through the thrust of a pilot research project that became a major activity of one of the categorical institutes of NIH.

Similarly, several years ago some initial pilot work at Johns Hopkins University School of Medicine by Dr. Robert B. Lewis who received $4,496 of biomedical research support funds for a pilot project to develop circuity for a new cardiac pacemaker. Within 6 months, the unit was developed and ready for implantation in dogs. This rechargeable cardiac pacemaker was selected as one of the top inventions of the year and has made a significant contribution to clinical medicine.

Early and detailed diagnosis is often the key to effective treatment of important diseases. At the Children's Hospital of Pittsburgh, Drs. Foley, Klein, and Agustin developed a simple test to detect cretinism in newborns. It has been possible to combine this test with other tests routinely performed in newborn infants at a cost of 25 cents per test. This test is likely to become a Public Health procedure employed worldwide with immense importance in human and financial terms because cretinism, if left untreated, leads to severe mental retardation.

These are some examples of the use of the biomedical research support funds by an institution to start a research project at a pilot level, bring investigators together and then move the research on to a more direct and forceful program supported by the categorical Institutes.

Mr. FLOOD. Do you know whether or not on that same research program on the gallstones they are stressing or trying to find out about just diet and nothing else? Rigidity of diet, the type of diet, as distinct from drugs or medicine?

Dr. BOWERY. Yes. There is some continuing work at the Mayo Clinic that is taking a look at a variety of factors.

Mr. FLOOD. What type of individuals within a given institution would receive funding on this biomedical research support grant program?

Dr. BOWERY. The funds are made directly available to the deans of the health professional schools and the vice presidents of research. However, we are insisting that they in turn establish a mandatory visible institutional review process within their own organizations so that the allocation and usage of these funds helps to insure flow to young investigators and pilot projects.

Mr. FLOOD. I was going to say, how do you monitor the expenditure of these funds I am talking about?

Dr. BOWERY. Each year we receive an annual scientific progress report from each grantee. We also receive an annual fiscal report that states how the funds were expended. In the revised program being carried out in 1976 we will reinforce this reporting by having some onsite program visitations by our advisory committees and staff where we feel there is not the proper balance that we feel is most appropriate for the use of these funds.

Mr. FLOOD. On the expenditure of funds, do you plan to spend these 1976 funds for the biomedical research support grants in accordance with the new formula and the guidelines that we all agreed to last year?

Dr. BOWERY. That is correct. We plan to make the biomedical research support awards about the first of April. However, we do not currently plan to initiate the companion biomedical research development award program during fiscal year 1976.

Mr. FLOOD. Also in your statement you say over 80 minority institutions receive support or will in 1977 under the minority biomedical support grant program.

Dr. BOWERY. That is correct.

Mr. FLOOD. That is in 1977. How does that compare with 1976?

Dr. BOWERY. It is essentially the same in 1976 as in 1977.

Mr. FLOOD. How many students and faculty are you supporting under this minority biomedical support program?

Dr. BOWERY. Approximately 1,300 students and about 600 faculty will be supported in 1976.

Mr. FLOOD. Can you give us some examples of the kind of research that you support under this particular program?

Dr. BOWERY. Here again, the range of research encompasses most of the different kinds of biomedical research activities that are being dealt with by the different Institutes of the NIH. We are actively working to try to interface these minority institutions with all the NIH categorical institutes.

We are supporting research on water pollution problems at the minority biomedical support research activity at Hilo, Hawaii. We have supported cancer research activities in some of the minority supported institutions in North Carolina. In addition, we have worked out special cooperative arrangements with the Heart and Lung Institute and with the National Cancer Institute to review some of our minority biomedical support projects to see whether they desire to fund those that are related to their scientific missions.

Mr. FLOOD. Have these minority institutions themselves, the ones that receive funds under this program, been able to attract support from any of the NIH institutions to expand their research efforts?

Dr. BOWERY. Yes.

Mr. FLOOD. You say yes. If the answer is yes, we would like a breakout.

Dr. BOWERY. I believe about 171 applications have been submitted to different funding sources, including NIH. About 96 of these have received approval which is about a 56 percent approval rate, generating about $2.3 million of other support.

Mr. FLOOD. Can you give us a breakout of the amounts received by each school?

Dr. BOWERY. Yes.

[The information follows:]

Other Biomedical Grant Support Received by Institutions Receiving a Minority Biomedical Support Grant (FY 1974)

Name of Institution	NIH Amount Awarded	Other Govt Agency Amount Awarded	Non-Government Amount Awarded	Total Amount Awarded
Shaw University Raleigh, North Carolina		33,000		33,000
Southeastern Oklahoma State University Durant, Oklahoma	34,500			34,500
Virginia Union University Richmond, Virginia			142,516	142,516
Xavier University New Orleans, Louisiana	12,000	35,000	7,000	54,000
Coppin State College Baltimore, Maryland			80,055	80,055
Delaware State College Dover, Delaware			23,203	23,203
University of Texas El Paso, Texas			14,000	14,000
Howard University Washington, D.C.	400,000	131,320		531,320
Johnson C. Smith University Charlotte, North Carolina		164,380		164,380
Albany State College Albany, Georgia	217,929			217,929
Bennett College Greensboro, North Carolina		301,959		301,959
Meharry Medical College Nashville, Tennessee	82,050	40,000		122,050
Winston-Salem State University Winston-Salem, North Carolina			1,500	1,500
Jackson State University Jackson, Mississippi		44,011		44,011
Bishop College Dallas, Texas			105,000	105,000
Central State University Wilberforce, Ohio		85,417		85,417
Grambling State University Grambling, Louisiana			1,500	1,500

Name of Institution	NIH Amount Awarded	Other Govt Agency Amount Awarded	Non-Government Amount Awarded	Total Amount Awarded
Knoxville College Knoxville, Tennessee			7,150	7,150
Southern University New Orleans, Louisiana			4,065	4,065
Fisk University Nashville, Tennessee		93,720	1,000	94,720
Dillard University New Orleans, Louisiana			25,000	25,000
New Mexico Highlands University Las Vegas, New Mexico			11,983	11,983
Hampton Institute Hampton, Virginia			700	700
Elizabeth City State University Elizabeth City, North Carolina			19,000	19,000
Virginia State College Petersburg, Virginia		58,649		58,649
Tuskegee Institute Tuskegee Institute, Alabama	23,126			23,126
California State University Los Angeles, California	66,000	53,500		119,500
Talladega College Talladega, Alabama		22,400		22,400
University of Hawaii Honolulu, Hawaii	40,000			40,000
	875,605	1,063,356	443,672	2,382,633

INFORMATION RESEARCH

Mr. FLOOD. How long has that computer system called Prophet been in operation?

Dr. BOWERY. It has been operating in its developmental stages for several years, and it is now moving into the more formal online-use stage. In 1976, there are about 100 different scientists located in 12 different user groups, in 9 States that are currently using Prophet.

Mr. FLOOD. What kind of progress are you making in getting these users to share the costs of the system?

Dr. BOWERY. In 1976 the users were sharing the costs of the system at approximately $6,000 per user group. We anticipate in 1977 that this will increase to approximately $10,000 per user group.

Mr. FLOOD. Do you intend to turn the system over to the National Library of Medicine?

Dr. BOWERY. No. Their systems tend to deal with hard copy documents. Prophet tends to deal with interaction of transfer of on-line information via the computer system.

We are hoping in 1977 to make a lot more of the software and hardware available to potential commercial vendors, and there may be an opportunity to spin elements of this system off into the private sector.

Mr. FLOOD. What percentage of the costs of the system will the users pay in 1977?

Dr. BOWERY. In 1977 it is estimated that each user group will pay $10,000 each and we have 15 such groups which will result in about $150,000 to $200,000 a year. The users will pay about 15 to 20 percent of the cost of the system.

PRIMATE RESEARCH

Mr. FLOOD. Again last year you remember we talked at some length about severe shortages of research animals, especially nonhuman primates. Does that situation still exist?

Dr. BOWERY. Yes; it does, but we are trying to attack it on several fronts. As I mentioned in my summary opening statement, we do have an Interagency Primate Steering Committee. It is carrying out three basic functions. We are establishing criteria for use in the review of research projects using primates.

Mr. FLOOD. You also told us that you were planning to award several contracts to study the feasibility of domestically breeding those primate species needed for these research purposes. What did you learn from these studies?

Dr. BOWERY. Yes, sir. The Division of Research Resources has released five primate breeding contracts. It is estimated within 5 years they will yield approximately 1,900 animals for use in extramural research programs. That is about 20 percent of the anticipated need.

Mr. FLOOD. We want you to develop that at length for the record.

Dr. BOWERY. I would be happy to do so.

[The information follows:]

FEASIBILITY OF BREEDING PRIMATES

It is feasible to breed nonhuman primates domestically in large numbers. The commonly used primates such as rhesus monkeys have only one baby per female per year. Of course, for various reasons a few animals may not have any offspring in a year. Among the primates only marmosets regularly produce twins. This makes breeding primates expensive. We estimate that it will cost $350

to $550 to produce a usable size rhesus monkey. This is almost twice as much as wild caught monkeys cost currently, but the cost of wild caught monkeys is increasing dramatically. In addition, the domestically bred animal will be of better quality, free of most diseases, of known age and ancestry. Projects underway make use of a variety of breeding systems including pair mated animals, harems consisting of 1 male and 8 females housed in small pens, groups of 50 animals housed in quarter-acre corrals, and free ranging groups of several hundred monkeys on islands. From this, we will learn which is the most efficient and economical system to breed primates. We currently have five breeding contracts that we estimate will cost about $800,000 to maintain in fiscal year 1977. Within 5 years, our high production estimate for these 5 projects is 2,300 animals annually. This is about 20 percent of the number used in NIH extramural research projects. We believe that eventually we will need to double primate breeding over our current efforts.

Mr. FLOOD. What species are in shortest supply?

Dr. BOWERY. The rhesus monkey is the major one. It is mainly exported from India. They have been cutting back. It is usually the animal of choice in a lot of biomedical research.

The squirrel monkey is another animal in short supply and we are trying to develop a breeding program for them.

Mr. FLOOD. How many of these domestic breeding contracts are you going to award in fiscal 1976 and how many in fiscal 1977?

Dr. BOWERY. We currently have five going in fiscal 1976. We anticipate the possibility of adding one additional contract in 1977.

Mr. FLOOD. What percentage of the total demand for these research primates will you be able to meet through this domestic breeding program?

Dr. BOWERY. Utilizing just the activities of the Division of Research Resources, we estimate in 5 years we would meet about 20 percent of the demand. In the intramural activities of the Division of Research Services they have at least three contracts which will produce about 1,100 animals which would anticipate meeting about 50 percent of their demand.

Mr. FLOOD. Are any of the NIH Institutes supporting any of these breeding primate colonies?

Dr. BOWERY. Four Institutes are developing colonies for their specific research needs, such as child health.

Mr. FLOOD. For the record identify these Institutes and then the dollars included and the kind of primates being bred.

Dr. BOWERY. Yes.

[The information follows:]

NIH INSTITUTES SUPPORTING PRIMATE BREEDING COLONIES

Some of the Institutes are supporting primate breeding projects to meet their own special research requirements. For example, the National Institute of Child Health and Human Development has a contract with the California Primate Research Center to produce pregnant animals in which the age of the fetus is precisely known. These pregnant animals are then shipped to Institute grantees for studies of fetal physiology and maternal fetal interactions. A total of about 325 pregnancies are produced per year. Cost of this breeding program is about $350,000 annually.

The National Heart and Lung Institute is supporting a project to produce about 20 chimpanzees annually which are free of antibodies to hepatitis B. These animals will be used in studies of how to prevent transmission of this disease through blood transfusions. This Institute is also supporting the breeding of about 500 animals to develop models for hypertension and atherosclerosis. The cost of these programs is about $1,500,000 annually and include funds for the development of the models.

The National Institute of Allergy and Infectious Diseases in cooperation with the Center for Disease Control and the Bureau of Biologics, Food and Drug

Administration, has contracts to breed chimpanzees and mystax marmosets for research on hepatitis. These animals are uniquely susceptible to hepatitis. About 230 animals will be produced annually. These programs cost about $400,000 annually.

The National Institute of Dental Research is supporting the breeding of primates at the Washington Primate Research Center. The fetal animals and infants are used to study the development of head and facial structures. About 50 are produced annually at a cost of approximately $25,000.

The National Institute of Neurologic Diseases, Communicative Disorders, and Stroke has contracts to produce about 200 timed pregnancies per year at a cost of about $100,000. These animals are all used to study the effects of various viruses on the production of malformed infants.

The primate breeding supported by these categorical Institutes is for animals with special characteristics required by specific research projects. The breeding programs of the Division of Research Resources produce general purpose animals for use throughout the NIH extramural research programs.

Mr. FLOOD. In addition to these breeding programs you are talking about, you support seven primate research centers?

Dr. BOWERY. That is correct, sir.

Mr. FLOOD. What kind of research are these centers performing?

Dr. BOWERY. They are conducting a wide array of research projects ranging from cardiovascular research at the Washington Center to behavior research at the Wisconsin Center, to infectious disease research at Tulane. The seven Centers have a population of about 7,800 animals in their colonies and about 3,000 of those animals are being used in breeding colonies. They anticipate producing approximately 1,000 infants over the next several years, which should meet about 50 percent of their needs.

Mr. FLOOD. Are these primate research centers to be utilized by researchers from the other NIH-supported projects?

Dr. BOWERY. Yes. There are approximately 750 investigators using these resources. These include investigators supported by funds from the National Institute of Mental Health, Food and Drug Administration, and other agencies within HEW as well as NIH which of course is the primary user.

Mr. FLOOD. Doctor, you are requesting an increase of $4,664,000 for the Clinical Research Program Center. Why is that increase necessary?

Dr. BOWERY. Basically it is to prevent a reduction of the number of centers we are able to support, and stave off a further reduction in the number of research beds over recent years because of the inflationary pressure.

Mr. FLOOD. How many more beds will you support by the increase?

Dr. BOWERY. Very few. Currently we are in the process of reducing our support and possibly phasing out some six centers. We anticipate of those six at least two to three may become competitive again.

Mr. FLOOD. Not many more beds.

Dr. BOWERY. We are not quite sure yet of the number of increased beds that may occur.

Mr. FLOOD. Doctor, why should we put a lot of money into inpatient facilities? Why not outpatient?

Dr. Fredrickson told us just the other day there are very impressive savings in the mounting costs of health care, in clinical investigations that can be realized on an out-patient basis. What about that?

Dr. BOWERY. Over the last 3 years we have increased the capacity of the clinical research centers for outpatient research. Sixty percent of the centers are now involved in outpatient activities. The current

estimate of outpatient research activities in 1976 includes some 47,000 patient visits, and we anticipate that rising to 75,000 in 1977.

Mr. FLOOD. Why should we put more money into inpatient facilities?

Dr. BOWERY. The facilities that you are contemplating putting more money into, encompass both inpatient and outpatient activities. It is not just going to inpatient; it is going to a mix of inpatient and outpatient activities. We are converting some of the inpatient space and facilities to outpatient activities, which tends to reduce some of the cost pressure on these centers.

Mr. FLOOD. We were very much impressed by the point made the other day.

Dr. BOWERY. If I may be bold, I would imagine Dr. Fredrickson in addition to claming this need for outpatient activities at the Clinical Center of the National Institutes of Health, was not decrying the need to maintain the strength of the inpatient activities at the Clinical Center.

Dr. FREDRICKSON. That is pretty bold, Mr. Chairman.

Mr. FLOOD. I just sat here.

Dr. BOWERY. I am saying we need and are developing a balanced inpatient-outpatient activity at the NIH campus as well as in the general clinical research centers.

Mr. FLOOD. Last year, you told us you were working with the other Institutes as well as with grantee institutions to insure they have a long line of investigators that are going to be waiting outside to use all those clinical research centers. What progress are you making in that area?

Dr. BOWERY. Last year this committee indicated there were at least nine centers that had what you considered low occupancy rates. We worked with those centers, and four of those nine have now increased their occupancy rate up to 60 to 80 percent.

We took a hard look at two of those who had quite low occupancy rates, and they were terminated because of their low scientific merit. In two other centers, of that nine, we reduced the bed support commensurate with the amount of occupancy pressure on those particular centers.

Mr. FLOOD. Give us a table for the record showing the number of the investigators using each center in 1975, 1976 and 1977.

[The information follows:]

Number of Investigators Using Each
General Clinical Research Center
In FY 1975 and FY 1976 1/

	1975 Actual	1976 Est.
Duke University	54	60
University of Alabama	67	74
Ohio State University	58	60
Johns Hopkins University	29	30
Washington University, St. Louis	72	74
University of Washington	103	102
Emory University	35	40
University of Pennsylvania	80	66
University of Michigan	31	41
Univ. of Southern California	29	31
University of Rochester	31	32
University of North Carolina	65	71
Cornell University	51	55
Northwestern University	29	34
Albert Einstein	22	28
University of Colorado	74	79
Johns Hopkins University	21	20
Montefiore Hospital	35	42
New England Medical Center Hospital	44	46
University of Chicago	28	30
University of Pittsburgh	33	33
Medical College of Wisconsin	42	45
University of Iowa	69	75
Georgetown University	46	30
University of Oklahoma	76	72
University of Puerto Rico	22	25
University of Utah	62	55
Virginia Commonwealth University	30	35
University of Cincinnati	24	22
University of Colorado	64	60
Stanford University	37	54
Mt. Sinai	56	55
University of Texas	64	61
St. Christopher's Hospital, Philadelphia	35	36
Beth Israel	49	50
University of California, San Francisco	58	75
University Hospitals of Cleveland	80	80
Stanford University	37	40
University of Florida	48	42
University of California, San Francisco	10	12
Children's Hospital, Pittsburgh	13	15
Children's Hospital, Los Angeles	36	20
Massachusetts Institute of Technology	14	14
Vanderbilt University	74	78
New York University, Bellevue	26	36
Rockefeller University	44	45
University of Vermont	48	48
Children's Hospital, Cincinnati	20	20
Yale University	120	110
Children's Hospital Medical Center, Boston	40	43
University of Washington	25	10

Number of Investigators Using Each
General Clinical Research Center
In FY 1975 and FY 1976 1/

	1975 Actual	1976 Est.
Baylor University	18	2/
Baylor University	39	45
Children's Memorial Hospital, Chicago	28	15
Case-Western Reserve	43	42
University of Tennessee	47	48
State University of New York - Syracuse	33	40
Children's Hospital of Philadelphia	31	40
University of Miami	34	40
Roswell Park	20	2/
Children's Hospital, District of Columbia	13	6
University of Missouri	52	44
University of Chicago	25	25
State University of New York, Downstate	13	18
University of Oregon	11	27
Bowman Gray	18	2/
Temple University	15	25
Baylor University	45	52
University of Minnesota	30	35
Harbor General Hospital	50	54
Boston University	10	20
Mayo Foundation	32	32
University of Mississippi	24	22
Children's Hospital, Buffalo	36	2/
University of Texas, Southwestern	68	73
Columbia University	10	60
University of Arizona	15	15
Johns Hospkins University	42	43
Albany Medical College	24	47
Indiana University	18	23
University of California-San Diego	23	35
Kansas University Medical Center	23	28
Scripps Clinic	19	25
University of Virginia	30	33
UCLA	64	74
Peter Bent Brigham	74	84
University of New Mexico		20
TOTAL	3,437	3,601

1/It is estimated that there will be approximately the same number of investigators using each center in FY 1977 as in FY 1976. Data is insufficient to make meaningful estimates for each center at this time.

2/ Estimate not included in total. Phase out

Mr. FLOOD. We are interested in maximum utilization. We don't like the idea that these centers are made captives by one or two investigators.

Dr. BOWERY. Yes. We are trying to insure there is an active and productive mix of investigators.

Mr. FLOOD. We talked last year about occupancy rates. Obviously if you get more of these investigators to use the facilities, the occupancy rates are going to increase. Has that been your experience in the last year?

Dr. BOWERY. Occupancy rates for last year are running about 70.4 percent based on the number of bed days and the amount of funds allocated. However, when we were trying to fit all of the 84 centers into our constrained fiscal envelope it became necessary even after making some bed reductions for low occupancy and some reduction in staff, we still had to apply about a 6 percent across-the-board reduction to all centers. Therefore, occupancy rates may not be running at the level anticipated, which was about a little over 70 percent.

Mr. FLOOD. Last year there were some few centers having chronically low occupancy rates. What is the current situation with those centers?

Dr. BOWERY. Four of those centers have increased their occupancy. We have terminated two of them, and we have reduced the bed support in two others. In one other, because they were making a physical transition, we felt it would be inappropriate to reduce their support until they got restabilized.

Mr. FLOOD. You also talked a good deal about third-party reimbursement to be collected by the centers. How much will you collect in 1976?

Dr. BOWERY. It was running approximately $4.3 million.

Mr. FLOOD. What do you expect to get in 1977?

Dr. BOWERY. Since we are not quite sure of the number of centers we will have, it is possible that this dollar level will be within this range or may be slightly higher.

Mr. FLOOD. Do you believe that this represents the maximum amount that these centers can collect or do you think there is a lot more to be done in collecting these third-party reimbursements?

Mr. BOWERY. I think it is the maximum that can be collected consistent with making a judgment of a number of patients that are in the centers for purely research purposes, and the number of patients that are there for a combination of research and care. I think if we try to force the issue to collect "the maximum amount," then we limit the investigator's choice of patient based on ability of the patient to pay, and not for the research purposes or research opportunities.

Mr. FLOOD. We are always concerned with getting the most out of this.

Dr. BOWERY. We are monitoring that very closely.

Mr. FLOOD. Mr. Michel?

BIOMEDICAL RESEARCH SUPPORT PROGRAM

Mr. MICHEL. Regarding the biomedical research support program for which you are proposing to discontinue funding, isn't this basi-

cally, when you come right down to it, a subsidy program for medical and other institutions?

Dr. BOWERY. The biomedical research support program is one of several mechanisms employed by the National Institutes of Health to pursue its mission to improve human health through development of new knowledge. This program serves biomedical research needs, such as pilot research, central shared equipment and facilities, and unanticipated needs and opportunities that are not met by other NIH research support mechanisms. The biomedical research support program complements other NIH programs, and increases their effectiveness and efficiency. Therefore, the biomedical research support program supports specifically the total NIH effort to develop new knowledge at non-Federal institutions. It is not a subsidy of the institutions themselves.

Mr. MICHEL. These grants are paid directly to institutions, are they not?

Dr. BOWERY. Biomedical research support grants are awarded to institutions as are other types of NIH grants. For each grant there is a program director, or a principal investigator, who is responsible to the NIH for proper administration of the grant.

Mr. MICHEL. According to your regulations, schools must have received at least $200,000 in Federal health research funds in order to be eligible. This includes overhead costs, does it not?

Dr. BOWERY. Yes; an institution must receive at least $200,000 in direct and indirect costs for allowable Public Health Service research grants in the latest complete Federal fiscal year to be eligible for a biomedical research support award, and such Public Health Service grant support must represent diversity, complexity, and breadth. Both of these requirements are considered necessary to assure that sufficient need for a biomedical research support award exists to justify a minimum grant, currently about $15,000.

Mr. MICHEL. So that the more effective an institution is in achieving a high overhead payment, the more it will be rewarded under this program, isn't that the case? The rich get richer, in other words?

Dr. BOWERY. The need for biomedical research support grants is generated at each grantee institution by the biomedical research supported by the Public Health Service because of its high scientific merit and expectation of significant research achievement. Therefore, the greater the amount of biomedical research, the greater is the need for biomedical research support grants support. However, the institutions with the largest biomedical research programs can absorb some of the costs of research requirements for which biomedical research support grants awards are intended. For this reason, the smallest institutions receive eight times as much biomedical research support grants support per dollar of other Public Health Service biomedical research support as do the largest institutions.

Consequently, the 10 largest institutions—in terms of biomedical and behavioral research—were estimated to have received 18 percent of the Public Health Service research support in 1975. These same 10 largest institutions will receive in 1976 only 6 percent of the total available funds from the biomedical research support program, under the provisions of the program.

The actual costs of performing biomedical research consist of both direct and indirect costs. Biomedical research support awards are based upon the level of allowable Public Health-supported research activity. The most equitable way to measure this level of research activity is in terms of the total cost, because the ratio of direct to indirect costs varies with the accounting practices of institutions.

Mr. MICHEL. Doesn't this program reward the recipients of Federal grant money at the expense of those who may receive most of their research money from private sources?

Dr. BOWERY. A major objective of the biomedical research support program is to strengthen the effectiveness and efficiency of Public Health Service supported research. Therefore, it is appropriate that the biomedical research support awards be based upon the levels of Public Health Service research support.

Mr. MICHEL. At one time, greater weight was given in awarding these grants to funds received from non-Federal sources, Why the change?

Dr. BOWERY. When the biomedical research support program, which was formerly named general research support program began in 1962, the award to each institution was based upon expenditures for biomedical research from both Federal and non-Federal funds. Greater weight was accorded expenditures from non-Federal funds as incentive to increase the role of non-Federal funds in biomedical research. This policy did not achieve its objective. Furthermore, differences in State laws and institutional accounting practices resulted in inequities. Differences in the relevance of expenditures to the concerns of the NIH, and in the rigor with which requests for support from various sources were evaluated for merit led to awards that were disproportionate to the needs and objectives of the biomedical research support program. Consequently, when the program was restructured in 1968, the entitlement base was changed from total biomedical research expenditures to allowable research grant awards from the NIH and National Institutes of Mental Health. In 1976 this policy was modified to include allowable research grant awards from the Public Health Service.

Mr. MICHEL. Under this program, an institution theoretically is prohibited from funding a research project that has been rejected by NIH, is it not?

Dr. BOWERY. Yes; this policy became effective in fiscal year 1976.

Mr. MICHEL. Could not the rejected grant be altered somewhat on its face to get around this requirement?

Dr. BOWERY. The decision regarding allocation of biomedical research support grant funds within the grantee institution rests with the program director, the principal investigator, with advice from a broad base of representation in the institution. This grantee review system is effective in the review of proposals that have not undergone review by the NIH peer review system. The grantee review system has the responsibility to determine whether a proposal, previously disapproved by the NIH peer review system has been modified in ways that correct the deficiencies responsible for disapproval and otherwise is sufficiently meritorious to receive support from biomedical research

support funds. There are good programatic reasons to believe that this new biomedical research support program policy will be effective. If not, it will be revised. We intend to monitor this policy.

Mr. MICHEL. Do you require an audit of how the institutions use their grant?

Dr. BOWERY. Detailed progress and expenditure reports are required of every grantee annually.

Mr. MICHEL. I think you had better provide for the record a detailed breakdown of how the largest recipients of these support grants disburse the grant money.

[Information follows:]

1974 Disbursement Data for Eight of the Largest Recipients of Biomedical Research Support Grants

Institution	Research Projects		Animal Facilities	Central Laboratory Facilities	Computer & Data Processing Facilities	Instrument Shop	Equipment For General Use	Student Research Participation		Other	
	Number	Amount						Number	Amount		
University of Minnesota (Medical School)	46	$166,752	$15,520	$38,355	--	--	--	--	--	---	
University of Wisconsin (Medical School)	26	76,672	21,075	30,965	$33	$3,576				Other Research Salaries (Professional, Technical,Support)	$73,779
University of Chicago (Pritzker School of Medicine)	27	158,099	--	--	--	--	--	$18	$14,800	---	
Stanford University (School of Medicine)	18	38,172	22,753	--	14,639	--	--	--	--	Laboratory Renovation Research Salary Increases Training	24,003 20,325 3,488
University of California, Los Angeles, (School of Medicine	50	226,974	--	--	--	--	$250	--	--	Support Salary for Human Subject Protection Committee	8,813
Washington University St. Louis,(School of Medicine)	40	199,711	39,468	--	3,792	--	4,804	39	23,100	---	

Institution	Research Projects		Animal Facilities	Central Laboratory Facilities	Computer & Data Processing Facilities	Instrument Shop	Equipment For General Use	Student Research Participation		Other	
	Number	Amount						Number	Amount		
Yale University (School of Medicine)	52	$90,521	$ 73,566	--	--	--	$151,295	12	$6,000	Salaries, Human Investigation Committee	14,821
										Research Salaries	4,752
										Medical Arts	2,039
University of Washington (School of Medicine)	45	150,473	--	--	38,045	--	3,935	--	--	Research Salaries	9,952
										Other Central Resource Costs	19,410

Mr. MICHEL. Moving to your primate research centers program, your statement makes reference to studies being done on "language-learning processes and related behaviors." What is this all about, and why is it being done as part of a medical research program?

Dr. BOWERY. Studies on language-learning processes and related behavior are being conducted on young chimpanzees at the Yerkes Primate Research Center in Atlanta, Ga. The research is being conducted to provide information which will result in a better understanding of how a child's first language skills are acquired. The information and techniques in language training developed from this work promises to have beneficial applications for both normal children and for thousands of children who fail to develop even minimal language skills due to sensory deficits, brain damage, or impoverished rearing conditions.

This research is being supported by a grant from the National Institute of Child Health and Human Development. The work thus far with a young chimpanzee has resulted in the refinement of a computer-controlled language training system. By use of this system, a young chimpanzee has mastered a variety of language-type skills. These include reading, sentence-completion, object naming, color naming, ability to engage in the exchange of novel sentences as used in conversation, ability to request the names of objects to be given to her, et cetera. The findings with this animal model are far above initial expectations. It is believed that the computer system now under development may be applied to the study of language processes of mentally retarded children with language deficits.

Mr. MICHEL. Why has there been a shortage of nonhuman primates for research use?

Dr. BOWERY. Primates have been imported from tropical and subtropical countries of South America, Africa, and Asia. Vast areas of nonhuman primate habitat in these countries are being destroyed by lumbering operations and conversion of the land to agricultural purposes. The cotton-topped marmoset and chimpanzees are important research animals and consideration is being given to declaring them endangered species. These factors coupled with worldwide concern for wildlife conservation have caused many countries to severely limit or prohibit primate exports. India, the prime source of the commonly used rhesus monkey, has been steadily cutting down its worldwide annual export quota from 50,000 in 1972, to 20,000 in 1975. Peru, Colombia, Brazil, and Guyana in South America have stopped exporting primates as has Thailand.

Another factor in primate shortages is that their use as a research animal in other countries has increased. The World Health Organization is encouraging polio vaccination programs in developing countries. The testing of polio vaccine for safety requires significant numbers of primates. In fact, one reason for reduction of the export quota of rhesus monkeys from India was that the Indians foresaw a need for the animals in their own polio program.

Mr. MICHEL. Are you making headway in overcoming this shortage?

Mr. BOWERY. Yes; we are. The Division of Research Resources is heavily involved in a recently formed Federal Interagency Primate Steering Committee. This committee is concerned with developmental

plans for domestic primate breeding programs. It has also taken steps to enhance the supply from countries of origin. The committee is also responsible for coordinating the use of primates for research in the United States, including the establishment of an allocation system if this becomes necessary.

We are currently supporting through contracts five projects that are designed to produce 2,300 primates annually for NIH extramural research. The Primate Research Centers supported by our Division breed an additional 1,100 animals for use in their research programs. In addition, the NIH intramural Division of Research Services, various NIH Institutes, the Food and Drug Administration, and the Center for Disease Control all have domestic primate breeding programs underway to meet their special requirements. In total, these projects will produce about 6,600 animals annually which is between 15 and 20 percent of the number used in the United States. We think we are about halfway with the domestic breeding program that will have to be developed.

GENERAL CLINICAL RESEARCH CENTER'S OCCUPANCY RATES

Mr. MICHEL. According to a table you provided us last year there is about a 75-percent occupancy rate for beds in your Clinical Research Centers. This is rather low, isn't it?

Dr. BOWERY. The 75-percent occupancy rate is considered to be optimal for a research ward, balancing efficiency of utilization with research protocol needs for available open beds. This occupancy is about 5 percent higher than the average for general hospitals in the United States.

Mr. MICHEL. Is anything being done to improve the occupancy rate, such as perhaps discontinuing funding for Centers with the lowest rates?

Dr. BOWERY. All Centers with occupancy rates significantly lower than the average are reviewed carefully each year, and some have been discontinued because of their low benefit-cost ratio. In others, with low occupancy but in which the existing activity has been judged to be of high scientific merit, steps are taken to broaden the scientific program or to reduce funding, either for fewer beds or for partial occupancy of existing beds.

Mr. FLOOD. Mr. Roybal.

MINORITY BIOMEDICAL SUPPORT PROGRAM

Mr. ROYBAL. Until the middle of last year, grants under this program went only to minority institutions. Now, they go to schools with large numbers of racial and ethnic minority students. Why was the change made?

Dr. BOWERY. The change was made because large numbers of ethnic minority students were not enrolled in traditional minority 4-year colleges but rather were enrolled in majority institutions or junior colleges in which minorities constituted a significant enrollment. To illustrate, only about one-third of black undergraduates were enrolled at predominantly black institutions, while one-third were enrolled at majority institutions and another one-third were enrolled in junior colleges; two-thirds of Spanish-speaking Chicano students, the major-

ity of Puerto Ricans, Cuban-Americans, and American Indians were enrolled in junior colleges. Other American Indians received whatever training they have on Indian reservations through work experience and not through the formal college-graduate school educational system.

Mr. ROYBAL. How has it worked out?

Dr. BOWERY. The grants to institutions with large numbers of racial and ethnic minority students has worked effectively. Although many more ethnic minority undergraudate students have benefited by the extension of the grant to majority 4-year institutions with large numbers of ethnic minorities, we have not as yet extended the program to any extent to junior colleges and American Indian tribes.

Mr. ROYBAL. Which groups have benefited?

Dr. BOWERY. The ethnic minority groups which have benefited by the extension of the grant to nontraditional minority institutions have been Spanish-speaking, American Indians, Asian Americans, and Black.

Mr. ROYBAL. Of the 293 undergraduate students who finished their training, how many were black, how many Spanish-surnamed, how many Asian Americans, how many American Indians, and how many women?

Dr. BOWERY. Of the 293 undergraduate students who finished their training during 1974, the ethnic and sex data on these graduates were not requested. However, during the spring semester of 1975, undergraduate students by ethnic breakdown receiving support from the minority biomedical support program include: Blacks—569, Spanish-speaking—196, American Indians—17, Hawaiian and other Polynesians—26, Orientals—5, and others—24, for a total of 837. Approximately 50 percent of these undergraduates are female.

Mr. ROYBAL. Tell us also by race, sex, and national origin, how many of these students entered medical, dental, or graduate schools.

Dr. BOWERY. Although we do not have the ethnic and sex breakdowns on minority biomedical support undergraduate students entering graduate, medical, dental, or other health-related schools, the career choices of 1974 graduates were as follows: 99 were admitted to graduate schools, 78 were admitted to medical schools, 13 were admitted to dental schools and 35 were admitted to other health-related schools, for a total of 225 participants. I would expect that the total of ethnic and sex percentages would be approximately the same as previously indicated.

Mr. ROYBAL. In the coming fiscal year, grants will be made at 80 schools. How many of those are in California?

Dr. BOWERY. There are four minority biomedical support grants in California; University of California, San Diego, California State, Los Angeles, University of California, Santa Cruz, and Charles R. Drew Postgraduate Medical School, Los Angeles.

Mr. ROYBAL. What type of monitoring program have you established to see that the terms of the grants under this program are being carried out?

Dr. BOWERY. The minority biomedical support program staff carefully monitors the progress of each minority biomedical supported program yearly and each project within a given program is monitored as to the progress it has made yearly toward the achievement of its

given objectives. Some of the criteria the minority biomedical support program staff uses are: The number of faculty publications resulting from the project research; the number of minority biomedical support faculty and student presentations at meetings, symposia, and seminars; the number of minority biomedical support student participants who enter graduate or other health-related schools; the number of grants attracted by minority biomedical support participating faculty; evidence of curriculum improvement in the minority biomedical support participating departments; evidence of improvement in faculty competence in minority biomedical support participating departments; and, evidence of increases in science majors as a result of the minority biomedical support program.

Moreover, the minority biomedical support program staff routinely make administrative staff visits to the institutions supported under the minority biomedical support program to insure that the institutional programs are operating smoothly and without difficulty. In addition, grants management personnel monitor all fiscal reports to determine that the funds at a minority biomedical support supported institution have been expended as approved. In this latter respect, both minority biomedical support professional staff and grants management staff work very closely together to assure that all phases of a minority biomedical support program are monitored effectively.

ANIMAL AND PRIMATE RESEARCH

Mr. ROYBAL. How much of your budget is spent on laboratory animal science and primate research?

Dr. BOWERY. The fiscal year 1977 budget for these animal resource programs is $20,036,000. Of this amount, $12,792,000 will be used to support seven Regional Primate Research Centers. These Primate Research Centers are used by approximately 750 investigators working on projects in cancer research, heart disease, reproductive biology, neurophysiology, mental retardation, infectious diseases, environmental health and other areas. The Centers provide ideal environments for the research utilization of the 8,000 primates of 40 species that are in their colonies. Primate research is important because for some studies they are the only animals with characteristics sufficiently similar to man so that results can be applied to human health problems.

A variety of laboratory animal science projects will be supported in the amount of $7,244,000. These projects include support for laboratories to diagnose and control diseases of research animals; projects to identify and describe new animal models of human health problems; stock centers to maintain and distribute established valuable animal models; projects to help institutions improve their animal care programs to meet the standards of the Federal Animal Welfare Act; training in laboratory animal science and medicine; and primate breeding contracts.

Mr. ROYBAL. Would you explain why it is difficult to get enough primates on which to do research?

Dr. BOWERY. Primates are difficult to obtain because wild populations are decreasing and worldwide use in medical projects is increasing. Destruction of habitat because of lumbering and conversion of land to agricultural purposes has caused a decrease in primate popula-

tions. This, coupled with concern for conservation, has caused many countries to drastically reduce export quotas or ban primate export entirely. Medical research and large scale polio vaccination programs in other countries has increased the use of primates. To help overcome the shortage of primates, we have started domestic breeding programs both through special contracts and through the Primate Research Centers program.

Mr. ROYBAL. How do you insure that the animal is healthy before he becomes the subject of research?

Dr. BOWERY. The question of animal health is an important one and the animal resources program has placed considerable emphasis on this area. The development of centralized programs of animal care has provided an important stimulus to uniform standards of laboratory animal care in many institutions. We have supported this development through institutional animal resource improvement grants at 90 institutions over the past 5 years. These funds have helped to renovate existing animal facilities, to purchase cages, cagewashers, and related equipment and to support the hiring of qualified professional and supervisory personnel. A basic goal of this activity has been to insure an appropriate environment for the maintenance of healthy animals. Since disease problems can occur, their prompt recognition coupled with appropriate control measures is important. We support laboratory animal diagnostic laboratories at a number of major research institutions. These laboratories have played an important role in establishing preventative health programs and insuring healthy laboratory animals. Several specialized resources have been established to provide diagnostic support to any institution requiring assistance. In addition, the animal resources program has been active in supporting individual research projects dealing with significant laboratory animal disease problems and environmental requirements. While much remains to be accomplished, we feel that significant progress in improved laboratory animal care has been made in recent years.

PATIENT-ORIENTED INVESTIGATIONS

Mr. ROYBAL. Under clinical research, you spoke of patient-oriented investigations. Are these people volunteers?

Dr. BOWERY. All of the research subjects on the General Clinical Research Centers are "volunteers," in the sense that they consent with free will and with clear understanding of their participation in the research project.

Mr. ROYBAL. How do you insure there is no coercion involved?

Dr. BOWERY. Great care is taken to avoid coercion or the appearance of coercion; consent to participate must meet the requirements of the Nuremberg code, which includes an assurance that the patients' right to treatment will in no way be degraded by refusal to cooperate in the research. The patients' rights are further protected by an institutional Committee on Human Experimentation, which includes representation of the population being served by the institution. This committee must evaluate and approve each protocol before implementation, and the minutes of the committee's deliberations are reviewed at regular intervals by General Clinical Research Center Staff, General Clinical Research Center Committee members, and outside consultants.

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Mr. ROYBAL. Do you ever test new drugs or methods on these people?

Dr. BOWERY. Yes, we do.

Mr. ROYBAL. Under what circumstances do you conduct the tests?

Dr. BOWERY. It is essential to test carefully any new drug or treatment on human volunteers before it is used in open medical practice, and this kind of testing is often carried out on a General Clinical Research Center. Therapies may be tested on patients only after they have been demonstrated safe and effective in animals, and shown to have a high potential benefit-risk ratio in volunteers. Therapies may be tested on patients only after they have been demonstrated safe and effective in animals, and shown to have a high potential benefit-risk ratio in volunteers.

Mr. ROYBAL. We have heard much discussion that one-fourth of hospital deaths are the result of diseases contracted in the hospital. In your 84 General Clinical Research Center's, is your record any better than this?

Dr. BOWERY. The majority of patients hospitalized on General Clinical Research Centers are either normal controls or individuals suffering from chronic diseases. There are also a small number of premature infants and patients with acute illnesses. General Clincial Research Centers are reviewed in the normal process of hospital accreditiation and must conform to all standards for patient care. Moreover each center is reviewed periodically by NIH to assure that the highest medical and scientific levels of standards for patient care and safety are maintained.

In fiscal year 1974 there were 26,417 admissions to General Clinical Research Centers, utilizing 229,754 patient days. During this period there were 164 deaths. Although specific questions referring to the cause of death of patients hospitalized on General Clinical Research Centers must be referred to the individual centers, our periodic reviews indicate that deaths in General Clinical Research Centers are the result of a normal progression of illness and not attributable to hospital-acquired complications.

Mr. FLOOD. Mr. Conte?

CLINICAL RESEARCH

Mr. CONTE. Do you feel that 83 General Clinical Research Centers are sufficient to support the ongoing efforts of NIH?

Dr. BOWERY. We feel that at the present time about 85 General Clinical Research Centers would be optimal to support the ongoing efforts of the NIH. Current budget priorities of the NIH as a whole have precluded this level of activity, however. As a result, individual Centers in the program have been asked to operate at the minimum effective level. There is a need to improve facilities and augment supporting personnel for outpatient studies at several Centers.

Mr. CONTE. Why were three of these Centers scheduled for phase out in 1976?

Dr. BOWERY. Currently, we are in the process of reducing our support and possibly phasing out six Centers in order to support only the most scientifically meritorious Centers with available funds. We anticipate of these six, two or three will reapply and compete success-

fully for program funds. Two or three new Centers of higher scientific merit will replace those Centers that had received phased out support in 1976.

CLINFO SYSTEM

Mr. CONTE. What will the one research and development contract cover under the biotechnology research section.

Dr. BOWERY. The contract will supply support for the CLINFO project which is a project to design and develop a simple computer system for clinical investigators.

Mr. CONTE. How would the CLINFO system operate, and how much would it cost?

Dr. BOWERY. The CLINFO project is a contract supporting a consortium of clinical and computer scientists from the Rand Corp., the University of Washington, the University of Oklahoma and Baylor University. This project is dedicated to the development and implementation of a stand-alone minicomputer system to enhance the quantity and quality of clinical investigations. The project should be completed in early 1978 at which time it should have produced a functional computer system which satisfies the computational needs of 90 percent of all clinical investigators. The value of this system is that it will be entirely dedicated to clinical research, unique among computer systems, and will be located in their research environment. The capabilities of the system include the storage, retrieval and analysis of research data. Within this framework it provides for: data entry into a study file for several forms of data screening and encoding; allowing the investigator to review and summarize his data including reviewing a single patient's data, and reviewing specified parameters for all patients in the study; allowing the creation of worksheets of data, for example, summarizations of data in tabular form from a variety of sources; the performance of a number of mathematical and statistical analyses, and produce reports, plots, and graphs from the worksheets; protection of the investigator's data from loss due to errors or computer malfunction and; privacy for both the investigator and the individual patients involved in the study.

This system is highly integrated and allows the user to perform a variety of sophisticated functions without the need to write computer programs. There is also the capability to make printed copies from all data stored in the system.

The development cost of the CLINFO project for four prototype systems is $2,300,000 over a 3-year period. At the end of this project one CLINFO system would cost approximately $40,000 per year, per center, with the cost of the computer amortized over a 5-year period.

PRIMATE RESEARCH

Mr. CONTE. Do the Primate Research Centers still depend on wild caught primates to a large extent?

Dr. BOWERY. Last year, the primate research centers produced about 1,100 animals for use in their research programs. This is slightly over half the animals that they required to maintain their colonies.

Mr. CONTE. What are the plans to expand the breeding capabilities of these centers?

Dr. BOWERY. Our long-term goal is to make the primate centers self-sufficient in terms of animal supply. This means maintaining large breeding colonies of the commonly used species, but just as important it means maintaining small breeding colonies of less commonly used species. Through these small breeding colonies, we will learn the technology of breeding many species of primates. These colonies can then be expanded if the need for a particular species increases. The history of primate research has been that a little used species will be discovered to be valuable for a particular type of research and the demand for it will increase significantly. The principal impediments to increasing the primate centers breeding program from meeting 50 percent of their needs to meeting 100 percent of their needs are financial and the fact that breeding stock of some species is difficult to obtain. We estimate that a 5-year program costing $1,500,000 per year would be necessary to obtain the facilities and breeding stocks and build the colonies up to the point of self-sufficiency.

BIOMEDICAL RESEARCH

Mr. CONTE. By cutting out the biomedical research support program aren't you wasting the $42.9 million we appropriated last year?

Dr. BOWERY. The goals of the biomedical research support program are directed toward needs that continue as long as biomedical research itself continues to be supported. The funds appropriated for the program in fiscal year 1976 will be used as effectively as in other years both to develop new knowledge for health and to enhance the effectiveness and efficiency of biomedical research supported by all other NIH programs.

PROPHET SYSTEM

Mr. CONTE. How much of the operating costs of Prophet do users pick up?

Dr. BOWERY. In 1977 it is anticipated that approximately 15 to 20 percent of the operating costs of Prophet will be contributed by the users. This will amount to about $150,000 to $200,000.

Mr. FLOOD. Thank you very much.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Research Resources

Amounts Available for Obligation 1/

	1976 Estimate	1977 Estimate
Appropriation:.....	$129,931,000	$92,342,000
Request pending.....	334,000	---
Subtotal, adjusted appropriations	$130,265,000	$92,342,000
Comparative transfers from:		
Office of the Director" for Standard level user charge.....	35,000	---
Total obligations.....	$130,300,000	$92,342,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $700,000 - 1977 - $800,000.

Research Resources

Budget Mechanism

	1976			1977		
	Number	FTE	Amount	Number	FTE	Amount
Grants						
Special						
General Clinical Research Centers	80		$42,184,000	83		$46,848,000
Biotechnology Resources	47		11,995,000	48		12,636,000
Animal Resources	85		18,510,000	82		17,902,000
Biomedical Research Support	450		42,957,000	--		--
Minority Biomedical Support	75		7,610,000	75		7,783,000
Subtotal	737		123,256,000	288		85,169,000
Fellowships						
Non-competing	3	6	144,000	5	14	266,000
Competing	--		--	--		--
New	2	2	30,000	4	6	99,000
Supplemental	--	--	--	--	--	--
Subtotal	5	8	174,000	9	20	365,000
Training						
Non-competing	3	10	160,000	--	--	--
Competing	--	--	--	--	--	--
New	--	--	--	--	--	--
Subtotal	3	10	160,000	--	--	--
Research and Development Contracts	21		3,593,000	18		3,511,000
Direct Operations			2,490,000			2,623,000
Program Management			592,000			627,000
Standard Level User Charge			35,000			47,000
TOTAL			130,300,000			92,342,000

1/ Full time equivalents

NATIONAL INSTITUTES OF HEALTH

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Division of Research Resources
(Dollars in Thousands)

	Research Grants										
	Regular Program		Specials		Training Programs		Laboratory and Clinical Research	Research and Development Contracts	Direct Operations	Program Management	Total
	Non-Competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships					
Clinical Research				42,184				435			42,619
Biotechnology Research				11,995				158			12,153
Laboratory Animal Sciences and Primate Research				18,510	160	174		2,000			20,844
Biomedical Research Support				42,957							42,957
Minority Biomedical Support				7,610							7,610
Chemical/Biological Information Handling Research				--				1,000			1,000
Research Management and Program Services									2,525	592	3,117
Total Obligations..				123,256	160	174		3,593	2,525	592	130,300

NATIONAL INSTITUTES OF HEALTH

CROSSWALK - 1977 Column of 1977 Justifications

Division of Research Resources
(Dollars in Thousands)

	Research Grants						Laboratory and Clinical Research	Research and Development Contracts	Direct Operations	Program Management	Total
	Regular Program		Specials		Training Programs						
	Non-Competing	Competing	Multi-disciplinary Centers	Other	Grants	Fellowships					
Clinical Research				46,848				435			47,283
Biotechnology Research				12,636				215			12,851
Laboratory Animal Sciences and Primate Research				17,902		365		1,769			20,036
Biomedical Research Support				--							--
Minority Biomedical Support				7,783							7,783
Chemical/Biological Information Handling Research				--				1,092			1,092
Research Management and Program Services									2,670	627	3,297
Total Obligations				85,169		365		3,511	2,670	627	92,342

SUMMARY AND EXPLANATION OF CHANGES

1976 Estimated Obligations	$130,300,000
1977 Estimated Obligations	$ 92,342,000
Net change	-37,958,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-ins:				
1. Annualization of 1975 Increase...	--	$77,000	--	$+23,000
2. Within-grade pay increases.....	--	19,000	--	+20,000
3. FTS rate increase.....	--	16,000		+8,000
4. Bureau of Employee Compensation..	--	4,000	--	+1,000
5. DHEW-NIH General Expense Fund....	--	105,000	--	+28,000
6. Increase cost of service and supply.....	--	57,000	--	+7,000
7. Increase cost of postage.....	--	26,000	--	+6,000
8. Program evaluation.....	--	454,000	--	+71,000
9. Payment to the NIH "Management Fund" for centrally furnished services.....	--	353,000	--	+46,000
10. Standard Level User Charge.....	--	35,000	--	+12,000
Subtotal.....				+222,000
B. Program:				
1. Special Programs				
a. Clinical research-increased cost of 83 continuing resource grants.....	--	42,184,000	--	+4,664,000
b. Biotechnology Research for 47 continuing grants and one new grant.....	--	11,995,000	--	+641,000
c. Minority Biomedical Support-for increased continuation cost for 75 grants.....	--	7,610,000	--	+173,000
2. Fellowships-for funding continuation cost and new awards.....	--	174,000	--	+191,000
3. Research and Development contracts for continuation costs.....	--	1,307,000	--	+149,000
				+5,818,000
Total increases.....				+6,040,000
Decreases:				
A. Built-in:				
1. One less day of pay.....	--	1,657,000	--	-6,000
2. Savings due to decrease in positions.....	77	1,680,000	-3	-36,000
			-3	-42,000

	1976 Base		Change from Base	
	Pos.	Amount	Pos.	Amount
B. Program:				
1. Special Programs				
a. Laboratory Animal Sciences and Primate Research-3 grants terminated after 1976	--	$18,510,000	--	$-608,000
b. Biomedical Research Support-phaseout of program	--	42,957,000	--	-42,957,000
2. Training - phaseout of the "old" training program	--	160,000	--	160,000
3. Research and development contracts-Reduction of the domestic breeding of subhuman primates	--	2,000,000	--	-231,000
Subtotal				-43,956,000
Total decrease				-43,998,000
Total net change			-3	$-37,958,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
184	Clinical Research ..	$42,558,000	$42,619,000	$47,283,000	+$4,664,000
	Pos.....	---	---	---	---
186	Biotechnology Research	12,135,000	12,153,000	12,851,000	+698,000
	Pos.....	---	---	---	---
188	Laboratory Animal Sciences and Primate Research..	17,376,000	20,844,000	20,036,000	-808,000
	Pos.....	---	---	---	---
192	Biomedical Research Support	---	42,957,000	---	-42,957,000
	Pos.....	---	---	---	---
194	Minority Biomedical Support	7,253,000	7,610,000	7,783,000	+173,000
	Pos.....	---	---	---	---
196	Chemical/Biological Information-Handling Research.	1,000,000	1,000,000	1,092,000	+92,000
198	Direct Operations..	2,439,000	2,490,000	2,623,000	+133,000
	Pos.....	57	60	57	-3
199	Program Management.	580,000	592,000	627,000	+35,000
	Pos.	17	17	17	---
	Standard Level User Charge	35,000	35,000	47,000	+12,000
	Pos.....	---	---	---	---
	Total Obligations.	$83,376,000	$130,300,000	$92,342,000	-$37,958,000
	Total Positions..	74	77	74	-3

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions	77	74	-3
Full-time equivalent of all other positions	5	6	+1
Average number of all employees	82	80	-2
Personnel compensation:			
Permanent positions	$ 1,416,000	$ 1,368,000	-$ 48,000
Positions other than permanent	80,000	100,000	+20,000
Other personnel compensation	12,000	12,000	--
Subtotal personnel compensation	1,508,000	1,480,000	-28,000
Personnel benefits	200,000	200,000	--
Travel and transportation of persons	120,000	120,000	--
Transportation of things	13,000	13,000	--
Rent-communications and utilities	113,000	131,000	+18,000
Printing and reproduction	65,000	65,000	--
Other services project contracts	3,593,000	3,511,000	-82,000
Payment to NIH Management Fund	353,000	399,000	+46,000
Other	706,000	850,000	+144,000
Supplies and materials	26,000	26,000	--
Equipment	13,000	13,000	--
Grants, subsidies and contributions	123,590,000	85,534,000	-38,056,000
Total direct obligations	$130,300,000	$92,342,000	-$37,958,000

Authorizing Legislation

Legislation	1977 Authorized	1977 Appropriation requested
Public Health Service Act, Title III, Part A. Section 301--Research and Investigation in general	Indefinite	$91,977,000 2/
Title IV, Part I - National Research Service Awards Act	1/	365,000 2/

1/ Authorization expired June 30, 1975; extension legislation is pending.
2/ Funding estimate only.

Research Resources

Table of Estimates and Appropriation History

Comparable

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
1967 1/	$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 4/
1974	88,626,000	133,316,000	133,994,000	126,935,000 5/
1975	82,700,000	124,370,000 6/	130,000,000	127,200,000
1976	81,093,000	129,100,000	132,000,000	
Items not considered		(334,000)	(334,000)	
1977	92,342,000			

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/ 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.
5/ Appropriation after reduction as authorized by P.L. 93-192.
6/ Excludes $1,430,000 for contract funds excluded in House allowance due to lack of authorizing legislation.

Research Resources

Table of Estimates and Appropriation History

Actual

Year	Budget Estimate To Congress	House Allowance	Senate Allowance	Appropriation
1967 1/	$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 4/
1974	88,632,000	133,322,000	134,000,000	129,426,000 5/
1975	82,700,000	124,370,000 6/	130,000,000	127,200,000
1976	81,058,000	129,065,000	132,065,000	
Items not considered		(334,000)	(334,000)	
1977	92,342,000			

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 Infections 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/ 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.
5/ Appropriation after reduction as authorized by P.L. 93-192.
6/ Excludes contracts not considered by House due to lacking authorization.

Justification

Research Resources

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Clinical Research.....	$42,558,000	$42,619,000	$47,283,000	$4,664,000
Pos.....	---	---	---	---
Biotechnology Research...	12,135,000	12,153,000	12,851,000	698,000
Pos.....	---	---	---	---
Laboratory Animal Sciences and Primate Research...	17,376,000	20,844,000	20,036,000	-808,000
Pos.....	---	---	---	---
Biomedical Research Support	---	42,957,000	---	-42,957,000
Pos.....	---	---	---	---
Minority Biomedical Support	7,253,000	7,610,000	7,783,000	173,000
Pos.....	---	---	---	---
Chemical Biological Information Handling Research	1,000,000	1,000,000	1,092,000	92,000
Pos.	---	---	---	---
Direct Operations	2,474,000	2,525,000	2,670,000	145,000
Pos.	57	60	57	-3
Program Management	580,000	592,000	627,000	35,000
Pos.....	17	17	17	--
Total	$83,376,000	$130,300,000	$92,342,000	-$37,958,000
Total Positions	74	77	74	-3

General Statement

The Division of Research Resources identifies and meets the contemporary research resources needs and challenges of the National Institutes of Health's biomedical research efforts. The Division has the responsibility to conceive, create, develop, support and make available the many different types of research resources required for the sophisticated health-related research performed by grantees nationally at academic institutions such as schools of medicine, dentistry, veterinary medicine, public health, pharmacy, as well as hospitals and research organizations.

A research resource supported by the Division of Research Resources can include skilled personnel - adequate technology tools, instruments and equipment- the necessary facilities and environment - or laboratory animals needed for the support of the fundamental research missions of the categorical Institutes of NIH.

The National Institutes of Health's responsibility for managing the research resources used by the Institutes' grantees is concentrated primarily in the Division of Research Resources which alleviates the necessity of duplicating these types of resources by each of the Institutes of NIH. This focus of management control creates a rational organization of these resources and increases the cost effectiveness of them by coordinating the sharing by many investigators of the use of the same resources for studying and researching various diseases and biomedical problems. These research resources also compliment other NIH forms of categorical research support by serving as crucial links for the many NIH-supported biomedical research endeavors. The Division administers six programs: Clinical Research, Biotechnology Research, Laboratory Animal Sciences and Primate Research, Biomedical Research Support, Minority Biomedical Support, Chemical/Biological Information-Handling Research.

Clinical Research

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Clinical Research.....	$42,558,000	$42,619,000	$47,283,000	+$4,664,000
Budget Mechamisn:				
Research Grants:				
Special.....	42,123,000	42,184,000	46,848,000	4,664,000
Number.....	80	80	83	+3
Research and Development				
Contracts.....	435,000	435,000	435,000	---
Number.....	2	2	2	---
Total	$42,558,000	$42,619,000	$47,283,000	+$4,664,000

Introduction: The General Clinical Research Centers Program establishes and maintains resource facilities for clinical investigation in order to increase knowledge of the cause, progression, prevention, and control of human disease. The Program supports 785 dedicated research beds in 84 General Clinical Research Centers (GCRCs), located in the teaching hospitals of medical schools throughout the nation. These Centers are staffed by 1,678 full-time research-trained personnel, including physicians, nurses, dietitians, technicians, and social workers. GCRC beds, set aside from the general care wards of the hospitals, are used as clinical research beds by scientists supported through the National Institutes of Health extramural research programs. Patient-oriented investigations at the GCRCs cover the medical research spectrum, including cancer therapy, organ transplantation, obesity, diabetes, disorders of growth, heart disease, high blood pressure, mental retardation, and drug metabolism.

The following describes the General Clinical Research Centers Program in 1975 and its projection through 1976 and 1977.

*More than 75% of the dedicated extramural research beds funded by NIH are supported by the Clinical Research Center Program.

*More than 1,500 investigators, supported by $280,000,000 in grants and contracts from the NIH categorical Institute programs, use the General Clinical Research Centers.

*Approximately 20 percent of the total NIH regular and special research grants totaling $1.4 billion involve investigators who use the General Clinical Research Centers.

*A total of about 3,900 biomedical researchers use the General Clinical Research Centers.

*An estimated 2,800 scientific papers and 1,400 abstracts are published each year reporting work performed in the GCRCs. One quarter of these publications concern studies on outpatients.

About 34% of the funds supporting the 1,500 NIH-supported investigators using the GCRCs come from the National Heart and Lung Institute; 26% from the National Cancer Institute; 19% from Arthritis, Metabolism and Digestive Diseases; 6% from Neurological Communicative Disorders, and Stroke; 6% from General Medical Sciences; 4% from Child Health and Human Development; and smaller fractions from Allergy and Infectious Diseases, Dental Research, the Eye Institute, and the Alcohol, Drug Abuse and Mental Health Administration.

One of the most important aspects of the GCRC program is that it provides an opportunity to study healthy "control" individuals, or patients with chronic illnesses not requiring hospitalization. These kinds of studies are fundamental to investigations of disease mechanisms and management. However, the scientific nature of the clinical research program sometimes requires that investigations be carried out using ill patients who do need to be hospitalized for treatment of their illnesses. For such patients, the Program supports the cost associated with the research only. Program policy permits collection of funds from private and third party funds for other patient care costs. In 1975, this policy resulted in the collection of more than $4,300,000 in third party payments.

A substantial savings mechanism which has been developed in order to reduce the cost to the Program of research performed in the GCRCs is an outpatient research program. Started in 1970, this permits the Centers to modify their facilities in order to include ambulatory subjects as research patients. The use of outpatients has enlarged the area of research that can be performed, and allowed a greater number of patients to be studied, treated, and maintained as a control group, providing additional research opportunities at lower costs.

Program plans for FY 1976: During 1976, the program supported 80 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.

Program Plans for FY 1977: The amount requested will provide support for approximately 83 Centers and will permit support for selected Centers which were scheduled for phase-out in 1977. The additional funds will be used to permit restoration of occupancy levels in existing Centers, to expand opportunities for outpatient research, and to selectively restore staff to some centers. A chart follows.

	1972	1973	1974	1975	1976 (Est.)	1977(Est.)
Inpatients	221,179	207,084	205,335	214,830	184,000	205,000
Outpatient Visits	24,658	36,309	48,845	60,000	(est.)47,000	75,000

Biotechnology Research

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Biotechnology Research.....	$12,135,000	$12,153,000	$12,851,000	+$698,000
Budget Mechanism:				
Research Grants:				
Special.....	11,977,000	11,995,000	12,636,000	+641,000
Number	47	47	48	+1
Research and Development Contracts	158,000	158,000	215,000	+57,000
Number.....	2	2	1	-1
Total	12,135,000	12,153,000	12,851,000	+698,000

Introduction: The Biotechnology Research Program interfaces the knowledge of the physical sciences, mathematics, and engineering to biology and medicine, for the advancement of biomedical research. The Program's resources combine the use of sophisticated and expensive instruments and equipment, complex methodologies, and unique human expertise to aid in the solution of important biomedical problems.

There are an estimated 993 NIH projects which use technological capabilities of the 47 Biotechnology Research Resources. The total value of these projects is approximately $64,000,000. The largest users of Biotechnology Resources based on latest figures available are grantees of the Heart and Lung, General Medical Sciences, Mental Health, Neurology, Cancer, and Arthritis Institutes.

Research Resource Sharing: The benefits of shared biotechnology resources are: (1) it obtains the support of a larger and more varied body of investigators and problems, (2) it maximizes the utilization of expensive instrumentation, (3) it increases collaboration among investigators from different institutions who have common research interests, (4) it increases the number and quality of researchers and institutions whose research will benefit from sophisticated biotechnology approaches to their biomedical activities. During FY 1975 the Biotechnology Research produced technological services and support to 993 investigations, of which 24 percent of the scientists (236) came from institutions outside of the host institutions where the shared resources was located.

Biomedical Engineering Resources: A Biotechnology resource specializing in microelectronics for health research was funded in 1974. The goal was to interact with health scientists in ways that lead to new and improved applications of micro-health research and patient care and to reduce the research overhead of medical scientists by providing ways to gain information which is attainable only with microelectronics techniques. This resource develops systems to control and study the regulation of body functions such as stress and strain of orthopedic appliances on humans; monitor intercranial pressure and cerebral spinal fluid pressures; and patient's condition after critical surgery or organ transplant, etc.

Artificial Intelligence Resources: Artificial intelligence is a part of computer science concerned with the symbol-manipulation processes. Scientists in this field use the computer to reach decisions and to solve problems through symbolic analysis and reasoning similar to how the human brain functions. Examples of artificial intelligence projects in progress, now and in 1977 are (1) development of a computer-based consultation system for diseases of the eye (initially glaucoma); (2) modeling the decision processes of medical experts in arriving at the selection of therapy for patients with bacterial infections; and (3) assisting the biochemist in interpreting molecular (cell) structures from mass spectral and other chemical information.

Program Plans for 1976: There were 47 grants and two contracts awarded in 1976 in the following categories: computer resource grants, biomolecular characterization resource grants, biomedical image and image processing resource grants, biomedical engineering, clinical research data management and analysis development contracts, and other miscellaneous categories.

Program Plans for 1977: Within the total funds available, continued support will be provided to approximately 48 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. There will be one research and development contract issued.

Presently there is no computer system available which can be used effectively to deal with the clinical investigator's problem in his clinical environment. If investigators had a suitable data management and analysis computer system available to them, it could reduce the duration of their studies and increase the number of published results.

The CLINFO (Clinical Information System) project is to design and develop a simple computer system for clinical investigators. Four contractors are developing different aspects of the system. The first system has been installed in a General Clinical Research Center (GCRC). As the work progresses, the CLINFO system will be evaluated at an additional two or three GCRC's to insure that the applications of this system are broad enough to be used by many clinical researchers throughout the country.

Another useful technology is high frequency nuclear magnetic resonance resources. These high frequency nuclear magnetic resonance instruments (NMR) are useful in biomedical research because they can detect and resolve most nuclear signals from biological materials in their natural state. These signals provide information that cannot be obtained from other instruments on the dynamic structure and functions of cells, organs and other biological material.

The use of NMR techniques offers the possibility of determining detailed knowledge of structure changes accompanying changes in biological function and will open areas to the design of new biologically active molecules and correction of metabolic (disease) defects which presently are not correctible.

Laboratory Animal Sciences and Primate Research

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Laboratory Animal Sciences and Primate Research	$17,376,000	$20,844,000	$20,036,000	-$808,000
Budget Mechanism:				
Research Grants:				
Special.....	15,842,000	18,510,000	17,902,000	-608,000
Number	74	85	82	-3
Training.....	334,000	334,000	365,000	+31,000
Number	8	8	9	+1
Research and Development Contracts	1,200,000	2,000,000	1,769,000	-231,000
Number	11	15	13	-2
Total	$17,376,000	$20,844,000	$20,036,000	-$808,000

Introduction:

The objective of the Laboratory Animal Sciences and Primate Research Program is to support resource projects which enable biomedical scientists to use effectively animals in health related research. Special attention is given to those animal resource activities that broadly support the research missions of the NIH Institutes. The program objectives are accomplished through: support of Primate Research Centers; laboratory animal disease control projects; projects to improve animal facilities and resources to meet the requirements of the Animal Welfare Act of 1970 (P.L. 91-579) and the HEW policies on the care and treatment of laboratory animals; and projects to develop, maintain, and increase colonies of special research animals. Training in laboratory animal science and medicine is also supported.

PRIMATE RESEARCH

The goals of the Primate Research Centers Program include: 1) To develop primate animal models for use in studies on diseases relevant to human health; 2) To provide scientific knowledge regarding problems of disease prevention, care, diagnosis and treatment of diseases, and breeding of primates; 3) To provide the excellent environments necessary for primate research which are not available or are very difficult to duplicate elsewhere; 4) To foster multidisciplinary research important to biomedical areas through Affiliate Scientist and graduate student programs; and 5) To reduce primate research costs by providing investigators with the expertise needed to avoid costly errors in selection and care of primate models, as well as in the proper design and conduct of experiments.

Subhuman primates are well recognized as the closest biological species to man. In recent years, wild-caught primates have become increasingly difficult to procure from countries of origin because of depleted resources, conservation movements, and man's general encroachment on their native habitats. In addition, they are expensive to purchase when available ($200 for an infant rhesus monkey), difficult to breed in captivity and costly to maintain ($1.50 per day). Wild-caught primates also carry many monkey diseases and are susceptible to certain human diseases because of their lack of natural or acquired immunity. Therefore, primates present many special problems which require considerable experience and management expertise in order to make them available for experimental use.

The Primate Research Centers Program supports seven Primate Centers located at Seattle, Washington; Beaverton, Oregon; Davis, California; Covington, Louisiana; Atlanta, Georgia; Madison, Wisconsin; and Southborough, Massachusetts. Each of these Centers provides a unique research environment where multidisciplinary biomedical research in many areas is being conducted. The Centers continue to provide national and international leadership in the field of medical primatology, with particularly significant contributions being made in areas including cancer-related research, reproductive biology, cardiovascular diseases, neural and behavioral disorders, drug addiction, infant respiratory diseases, and kidney diseases.

A total of 152 core staff scientists are currently conducting research studies on 111 grants and contracts totalling $6.6 million. A total of 817 scientific publications and books resulted from this research in 1975. In addition, 432 collaborative scientists from numerous universities are conducting research at the Centers on 127 grants and contracts totalling $11.0 million. A total of 725 scientific publications and books resulted from this research in 1975. The Centers also are providing the research environment for 163 graduate students to undertake their thesis research.

The national problem of obtaining sufficient subhuman primates for research purposes has now reached a critical stage. To meet this need, it has become necessary to significantly increase the domestic production of primate species used in biomedical research. The Primate Centers are providing tne necessary basic knowledge for establishment of large primate breeding programs and are now developing plans to expand their own breeding programs to eventually meet all of their own research needs. The Centers are now producing approximately 50 percent of their requirements for experimental primates, with a total of 1,055 infant primates produced during 1975. Approximately 7,800 primates are currently maintained within the seven Centers with 3,200 animals in breeding colonies.

Examples of studies currently in progress at several of the Primate Centers include the following: sudden infant death syndrome; social and behavioral effects of malnutrition on young primates; effects of environmental pollutants on respiratory function; metabolic bone disease studies; biological effects of exposure to polychlorinated biphenyl compounds; and language learning process behavior study.

LABORATORY ANIMAL SCIENCES

Research Animal Diagnostic and Investigative Laboratories:

The objectives of these laboratories are to provide for improved animal health programs through investigation of naturally occurring laboratory animal diseases, to support indepth studies resulting in new information on disease processes and their etiology, and to aid in the elucidation of new laboratory animal models of human disease. The laboratories also provide a base for training young investigators in laboratory animal medicine and comparative pathology. There are 13 active programs and this level of activity is expected to continue in the coming year. By strengthening an institution's animal health program, the laboratories make a direct contribution to approximately 885 NIH supported research projects using animals with total funding of nearly $56 million. In addition, seven research projects are being supported on important disease complications of animal research.

Animal Facilities and Resources Improvements:

A major program area during the past four 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 the DHEW policy on "Animal Welfare" (issued May 14, 1973). A total of 89 new grants and approximately $10.3 million have been awarded during this period. 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. The amount of funded research involving the use of animals and the sources of funding are important factors in establishing funding priorities. It is estimated that there are 1,433 projects ($90 million current annual funding) involving the use of animals which are supported by NIH at those institutions with currently active resource improvement projects.

Research Animal Models:

The objective of this program area is to define, characterize and exploit the relevant biological attributes of selected animals for which there is evidence of potential usefulness in several areas of biomedical research. Full exploitation of the potential usefulness of new animal models normally requires the efforts of investigators in several disciplinary areas over an extended period of time. Approximately 20 projects have been supported over the past several years, and this level of activity is expected to continue during the next year.

Colonies of Special Research Animals:

These projects provide for maintenance and production of special animal species and strains which serve as national resources. One of the most important activities in this area has been the establishment of colonies for the domestic production of nonhuman primates. Widespread habitat destruction and concern for conservation of animals has caused many nations to severely restrict the number of nonhuman primates that they will allow to be exported. For example, India has reduced by 60 percent the number of the commonly used rhesus monkeys that can be exported. Because nonhuman primates are the closest animal relatives of man, they are extremely important research animals. Therefore, the program will support approximately eight domestic primate breeding colonies which will eventually supply approximately one-fifth of the requirements of NIH supported extramural investigators.

Training:

There is a significant shortage of well trained people in the field of Laboratory Animal Sciences with vacant positions outnumbering available candidates by four to one. National Research Service Awards allow individuals to receive support for research training which prepares individuals to provide professional care of the many species of laboratory animals, to manage central animal resources, and to give special assistance to investigators through superior knowledge of laboratory animal biology and understanding of research methods. In addition, graduates are prepared to participate in the teaching of graduate students and young investigators and to pursue their own research interests either as independent investigators or as a member of a research team. Currently available figures indicate that 110 trainees and fellows have completed training since the inception of training activities. The majority (62) are functioning as directors or staff members of a vivarium; 41 are engaged in research or are obtaining additional training; and 7 are engaged in public health and other activities. Retention in the field of laboratory animal medicine has been excellent, emphasizing the career orientation provided by the training and the continuing need and opportunities available for such individuals.

Program Plans for 1976:

Seven Primate Research Centers conducting research in a number of biomedically important areas were supported. These Centers were used by 747 biomedical investigators. Twenty laboratory animal disease control projects helped maintain the health of animals used in 885 NIH supported research projects. Thirty-eight institutions with 1,433 NIH research projects were assisted in bringing their animal care programs up to optimum standards. Twenty special animal colonies and animal model projects of critical importance to 63 NIH research grants also received support. Approximately 8 individual and institutional National Research Service awards will be funded.

It is estimated that 78 Laboratory Animal Science resources and seven Primate Centers will receive support. There will be 15 research and development contracts issued, including 6 primate breeding projects targeted to produce 2,500 animals annually.

Program Plans for Laboratory Animal Sciences and Primate Research for 1977:

With the total funds available, support will be provided to 7 Primate Research Centers and 75 Laboratory Animal Science projects. The Laboratory Animal Science projects will include 20 on disease control, 33 on improvement of institutional animal resource programs, and 22 on special animal colonies and animal model development. A total of 20 individuals will receive training through 9 individual and institutional National Research Service awards. There will be 13 contracts issued including those on primate breeding.

Biomedical Research Support

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Biomedical Research Support Grants.....	---	$42,957,000	---	-$42,957,000
Number	---	450	---	-450

Introduction:

The Biomedical Research Support (BRS) Program, formerly known as the General Research Support Program, is authorized by Public Law 86-798. The size of the BRS awards are determined by a formula applied to the total amounts of other Public Health Service (PHS) research-supported grants awarded to each eligible institution.

The formula is designed so that institutions with the smaller total of Public Health Service research-supported research, receive up to eight times as much, proportionately, of the Biomedical Research Support compared to the institutions who receive the largest amounts of Public Health Service research support. However, the largest institutions receive the largest actual dollar awards.

Program Plans for 1976:

The Subcommittees on Appropriations for the Departments of Labor and Health, Education, and Welfare of both the House of Representatives and the Senate, in their reports on the 1975 appropriation, requested that a study be conducted of the existing General Research Support Program to determine whether changing circumstances and the passage of time had resulted in a need to change policies governing the allocation and usage of grant funds. A report of the study proposing the BRS Program and its companion Biomedical Research Development (BRD) Grant Program was transmitted to the Chairmen of the Subcommittees on April 9, 1975, by the Assistant Secretary, Comptroller, DHEW. In the transmittal, the DHEW position for phasing out the Program was indicated--

"-- 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 competititon for funds and peer group scientific review--are seen as a superior mechanism for the distribution of available biomedical research funds."

The Department's position remains unchanged.

The basic recommendations concerning revision of the Program were accepted by both Committees on Appropriations, and will be implemented in 1976 with approximately 450 awards to health professional schools, other academic institutions, hospitals, health departments, and nonprofit research organizations pending an apportionment of FY 1976 funds.

The recommendation of the Appropriations Committees to initiate a Biomedical Research Development Grant Program for new, small, and developing institutions is included in the House and Senate passed appropriations bill, but actual implementation has been delayed due to the provisions of the FY 1976 continuing resolution.

Program Plans for 1977:

Budget restraints in recent years have required a re-evaluation of NIH programs to determine what levels of support should be maintained and where reductions can be made with least adverse effect. Under present circumstances, other NIH biomedical research programs and activities are considered to have a higher priority than BRS Program. Consequently, funds are not proposed for this acitivity in 1977.

Minority Biomedical Support

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Minority Biomedical Support	$7,253,000	$7,610,000	$7,783,000	+$173,000
Number	70	75	75	---
Budget Mechanism:				
Research Grants:				
Special	7,253,000	7,610,000	7,783,000	+173,000
Number	70	75	75	---

Introduction:

The Minority Biomedical Support (MBS) Program objectives are to increase the numbers of ethnic minority faculty, students, and investigators engaged in biomedical research. This can be accomplished by broadening the opportunities for participation in biomedical research of ethnic minority faculty and student investigators, and by providing an appropriate setting in which these goals can be accomplished. The MBS Program is the major focus and effort of the NIH to involve minorities in biomedical research.

The MBS Program is unique within the NIH. Since its initiation, the MBS Program has been expanded and modified. Institutions now eligible include two-year colleges, and colleges and universities having large numbers of ethnic minority students, in addition to the traditional 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 third Annual Xavier University MBS Symposium in New Orleans, in May 1975, faculty and students supported through the MBS Program presented 290 papers in biomedical sciences.

The funds for the MBS Program are awarded for support of initiation of biomedical research projects and support of ongoing research projects by faculty and students at minority institutions. Such support has resulted in accomplishments such as the following:

At the Catholic University of Puerto Rico, a crude extract has been isolated which exhibits insulin activity. This extract comes from an insect and may show promise in the treatment of diabetes. As a result of sole support from MBS funds, two investigators from the University of Puerto Rico have developed a chemical that shows promise (in preliminary tests) for the treatment of a schistosomiasis, a blood fluke (worm) disease.

One of the investigators supported by the MBS Program at Atlanta University has received a Research Career Development Award from NIH in recognition of that investigator's promise as an outstanding biomedical researcher. Similar grants have been approved for funding at two other institutions supported by the MBS Program.

The Minority Biomedical Support Program has made substantial progress since it started just a few years ago. It is now a well-functioning program able to turn out excellent results from its awards. The present accomplishments of the program have been summarized by the data presented in the table following.

MBS ACCOMPLISHMENTS DATA FOR FY 75

Numbers of Participants - 1975

Faculty	589
Undergraduates	1,008
Graduate Students	184
Postdoctoral	3
TOTAL	1,784

Student Participants

Number of Student Participants Graduated	293	
To Advanced Training:		
Number of Student Participants Admitted to Medical School	78	
Number of Student Participants Admitted to Dental School	13	
Number of Student Participants Admitted to Graduate School	99	
Number of Student Participants Admitted to other Health Related Schools	35	
Total to Advanced Training	225	= 80%

Research Results

Total Projects Supported	410
Number of Publications	75
Number of papers presented (including abstracts)	358

Other Grant Support Generated as Result of MBS Program

Number of applications submitted	171
Number of applications approved in 1975 only	96

1975 Grant Support from sources other than MBS*

	Number	Amount
NIH	14	$ 875,605
Other Government	61	1,063,356
Non-Government	41	443,672
TOTAL	116	$2,382,633

* includes applications approved in 1975 and previous years

Program Plans for 1976:

An estimated 75 grants supporting 80 minority institutions will be awarded in 1976. Grantees include 58 schools with a predominance of Blacks, 17 schools with a predominance of Spanish-speaking students, 3 schools with a large number of American Indians, and 2 schools with a large number of Hawaiian/Polynesian students. Six-hundred faculty and 1,300 students will be supported from the MBS Program.

Program Plans for 1977:

With the total funds requested for 1977, continued support will be provided to an estimated 75 grants for institutional research programs involving minority scientists in biomedical research and exposure of minority students to the challenges and opportunities of biomedical research.

Chemical/Biological Information-Handling Research

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Chemical/Biological Information-Handling Research	$1,000,000	$1,000,000	$1,092,000	+$92,000
Number.....	2	2	2	---
Budget Mechanism: Research and Development Contracts	1,000,000	1,000,000	1,092,000	+92,000
Number	2	2	2	---

Introduction:

The Chemical/Biological Information-Handling Research (CBIHR) Program develops new computer-based tools for handling research information about chemical substances and their biological effects. These tools are made available via a telecommunications network to a community of scientists distributed nationwide. These scientists are seeking to understand how chemical substances interact with human and animal systems.

At present, it is generally impossible to predict how a given chemical substance will interact with a given biological system under a given set of circumstances. As a result, the development of new drugs is hindered, and the most effective use of existing drugs often is not realized. This reflects both a need for more basic biological and chemical knowledge and a need for more powerful techniques for organizing and manipulating research information. As scientists succeed in learning to predict how a new drug or other chemical substance will affect experimental animals and humans, the resulting new knowledge will do much to reduce the time and costs associated with new drug development, avoid side effects of existing drugs, and generally improve health care delivery.

The heart of the CBIHR Program is a unique research resource called PROPHET. It is the most nearly comprehensive array of computer tools for research on chemical/biological interactions ever integrated into a single System. Because few, if any, research institutions can justify having a System of such scope and power entirely to themselves, PROPHET is operated as a national shared research resource. Its services are allocated competitevely via a peer review process. Users help to defray the operating costs of the System with funds from their own research grants and contracts.

Assisted by PROPHET and its highly skilled staff, scientists are able to deal with larger amounts and more complicated types of data than is possible by hand. They can conduct experiments that would be impossible or impractical in the absence of these advanced computer tools. And, because they share the same facility even though they are widely separated geographically, they can readily exchange data and computer programs and thereby avoid needless duplication of effort.

There are now over 100 PROPHET users and 12 user groups. They are located in Boston, Massachusetts; New York, New York; Buffalo, New York (2 user groups); Pittsburgh, Pennsylvania; New Haven, Connecticut; Evanston, Illinois; Seattle, Washington; Cleveland, Ohio; Menlo Park, California; San Francisco, California; and Bethesda, Maryland. Steady growth in the number of users and number of sites is expected to continue. Moreover, new tools are continually being added as a result of the users' experiences and suggestions.

Program Plans for 1976:

The CBIHR Program has (a) enlarged the community of PROPHET users to over 100 scientists at 12 sites in 9 states; (b) made possible the creation of a unique computer data bank containing the latest research information on the three-dimensional shapes of chemical substances known to affect fertility, child development, and a host of other life processes; (c) facilitated research on a wide variety of medical problems such as how diseased kidneys handle drugs and other blood constituents, how alcohol and other drugs affect the brain, and how the body is able to react selectively against specific foreign chemical substances as in the case of an allergic response or the rejection of a transplanted organ; and (d) continued to have PROPHET users share in the operating costs of the System at approximately $6,000 per user group per year. In 1976 two contracts will be issued.

Program Plans for 1977:

The CBIHR Program will (a) expand the community of PROPHET users to approximately 125 scientists at 15 sites; (b) make possible the continuing development and broad dissemination of a unique data bank on the chemical structure of the specialized proteins which are a key component of the body's immunity against foreign substances; (c) facilitate new investigations of a wide variety of clinically important chemical substance such as those which are involved in the regulation of blood pressure, those which affect the body's basic metabolic rate and those which destroy or retard the growth of cancer cells; and (d) increase to approximately $10,000 per user group per year the extent to which PROPHET users share in the operating costs of the System. In 1977 two contracts will be issued.

Direct Operations

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Direct Operations	$2,474,000	$2,525,000	$2,670,000	+$145,000
Positions	57	60	57	-3

Introduction:

This activity supports the Division of Research Resources' extramural program staff which administers and manages the research resource grants and contracts, plus the formula grants of the Biomedical Research Support Programs. There are no matching requirements. The Programs' staff are responsible for the planning and development of their programs which will best serve the Program's mission and the health mission of NIH. They review and evaluate the grant applications for presentation to the National Advisory Research Resources Council. They also provide assistance and act as liaison with applicants and grantees, and provide continuing surveillance of the grants. Scientific and technical review of each of the grants is also provided to assure that the scientific mission of the Programs are fulfilled.

Program Plans in 1976 and 1977:

This activity will continue to administer, manage, and review the grants and contracts. Planning, development, and scientific review will be continued to assure that the Programs will contribute to promote NIH's health mission.

A total of 766 awards are expected to be issued in 1976 and 317 awards are estimated to be issued in 1977. No funds were requested in 1977 budget for the Biomedical Research Support Program and has caused a decrease of 407 grants in 1977. There are 190 site visits planned each year to new applicants and to current awardees.

Several workshops are to be arranged nationally for the advance study of sophisticated technologies and their application to the advancement of biomedical science.

The staff will attend and participate in several National Society meetings and will also sponsor a symposium for the Division's Minority Biomedical Support Program at Xavier University in New Orleans at which an expected 270 papers on biomedical sciences are to be presented. Two Directors Meetings are planned for 1976 so that the directors who administer the grants which they receive from NIH will be able to discuss their joint problems together and will also allow the Programs to explain, train, and elucidate their goals and policies.

The Division's staff will continue its active participation in the Inter-Agency Primate Steering Committee which is developing plans for the provision of adequate primate supplies for both the NIH's extramural and intramural research efforts.

Program Management

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Program Management	$580,000	$592,000	$627,000	+$35,000
Positions.....	17	17	17	---

Introduction:

This activity provides the general administration, planning, direction, and coordination of the Division's Programs.

Program Management funds the Office of the Director and related staff and includes the Office of Science and Health Reports. The six programs which they administer are Clinical Research, Biotechnology Research, Laboratory Animal Sciences and Primate Research, Biomedical Research Support, Minority Biomedical Support, and Chemical/Biological Information-Handling Research.

Program Plans in 1976 and 1977:

The Division will continue its "interfacing" meetings with the officials of the categorical Institutes to diffuse information about the types and capabilities of ongoing Division-supported resources. In addition, the Division acquired information about the current needs and the future plans of the Institutes. This increased interaction will assure the Division's Programs are responsive to the needs of the investigators supported by NIH and will also aid in the forward planning of new resource development activities.

This activity will continue to provide the overall direction, management, administration, and coordination of the Division's Programs.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Clinical Research

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$42,619,000	Indefinite	--	$47,283,000

Purpose: The General Clinical Research Centers program provides the Nation's clinical investigators with the specialized clinical research resources and facilities needed to extend medical knowledge and translate the latest laboratory discoveries into improved care for patients. The authorizing legislation is Public Health Service Act, Title III, Part A.

Explanation: This program supports the General Clinical Research Centers (GCRCs) throughout the nation. These GCRCs are physically discrete research units, located in the university affiliated hospitals, ranging in size from four to thirty beds, with an average size of 10 beds. The program provides support for a fixed number of beds and a staff of specially trained nurses, dietitians, laboratory personnel, and a physician director. Each GCRC is a specialized research unit with bedrooms, bathrooms, treatment rooms, core laboratories, metabolic diet kitchens, patient lounge, nurses' station, and conference rooms.

Applications to the Program are reviewed by the General Clinical Research Centers Advisory Committee, program staff, and the National Advisory Research Resources Council. Staff determines priorities of awards on the basis of recommendations by 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 project periods of three to five years. There are no matching fund requirements.

Accomplishments in 1976: During 1976, the program supported 80 clinical research centers in two-thirds of the teaching medical institutions of the nation. Most centers can accommodate both children and adults, but 20% of them specialized in pediatric problems. Originally inpatient units, the centers have been allowed to modify their facilities in order to utilize ambulatory patients as research subjects. About 60% of the GCRCs now include an outpatient clinical research program.

Objectives for 1977: The amount requested will provide support for approximately 83 Centers and will permit support for selected Centers which were scheduled for phase-out in 1977. The additional funds will be used to permit restoration of occupancy levels in existing Centers, to expand opportunities for outpatient research in selected Centers, and to restore staff selectively.

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NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Biotechnology Research

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$12,153,000	Indefinite	--	$12,851,000

Purpose: The Biotechnology Research Program interfaces the knowledge of the physical sciences, mathematics, and engineering to biology and medicine for the advancement of biomedical research. The Program's resources combine the use of sophisticated and expensive instruments and equipment, complex methodologies, and unique human expertise to aid in the solution of important biomedical problems. The authorizing legislation is Public Health Service Act, Title III, Part A.

Explanation: The Biotechnology Research Program has 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. The modern trend is for the resources to be specialized to specific research needs rather than to have just general biomedical research application. The Program's grants are awarded in yearly increments for a project period up to five years and are eligible for renewal. The grant applications are reviewed by several study components (one for each technology in the Program). Contracts are also used to support projects.

Accomplishment in 1976: There were 47 grants and two contracts awarded in 1976 in the following categories: computer resource grants, biomolecular characterization resource grants, biomedical image and image processing resource grants, biomedical engineering, clinical research data management and analysis development contracts, and other miscellaneous categories.

Objectives for 1977: Within the total funds available, continued support will be provided to approximately 48 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. There will be one research and development contract issued.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Laboratory Animal Sciences and Primate Research

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$20,844,000	Indefinite	--	$20,036,000

Purpose: The Laboratory Animal Sciences and Primate Research Program assists in providing animal resources for biomedical research and provides special research centers for biomedical and behavioral research using nonhuman primates. The authorizing legislation is Public Health Service Act, Title III, Part A.

Explanation: Primate Research Centers are supported to provide a specialized environment where research with these expensive and difficult to handle animals can be conducted in an efficient manner. Nonhuman primates are valuable research subjects because they are biologically more similar to human beings than are other animals. The Primate Research Centers are heavily engaged in research on infectious diseases, reproductive biology, cancer, heart disease, and the nervous system.

Project grants and contracts 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, training in laboratory animal science and medicine, and domestic primate production.

Accomplishments in 1976: It is estimated that 78 Laboratory Animal Science resources will receive support and in addition 7 Primate Centers will be supported. Approximately 8 individual and institutional fellowships will be awarded in 1976. There will be 15 research and development contracts issued, including primate breeding contracts.

Objectives for 1977: The FY 1977 budget will support 7 Primate Research Centers and 75 Laboratory Animal Science projects. These resources will in turn be used by approximately 2,800 NIH supported research projects and a number of projects supported by other agencies. There will be a continued effort to increase primate breeding to 2,500 animals to partially offset restrictions on importation. A total of 13 contracts including those on primate breeding are planned. Approximately 9 individual and institutional National Research Service awards will be funded.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Biomedical Research Support

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$42,957,000	Indefinite	--	--

Purpose: The Biomedical Research Support (BRS) Grant Program is authorized by Public Law 86-798 which provides for grants-in-aid "to public or nonprofit universities, hospitals, laboratories, and other institutions for the general support of their research and research training programs . . . ." The authorizing legislation is Public Health Service Act, Title III, Part A.

Explanation: The BRS Program provides funds to eligible institutions for their self-determined and flexible use in support of biomedical and behavioral research for purposes such as support of emerging research opportunities and pilot studies, sudden and unpredictable research needs, support of new and young investigators, and improvement of institutional research resources both physical and human. The grant project is a formula grant and has no matching requirement.

Accomplishments in 1976: Funds available in FY 1976 will provide support for approximately 450 health professional schools, other academic institutions, hospitals, health departments, and other nonprofit research organizations under program revisions approved by the Congress.

The ten largest institutions (in terms of biomedical and behavioral research) were estimated to have received 18 percent of the Public Health Service research support in 1975. These same ten largest institutions will receive 6 percent of the total available funds from the Biomedical Research Support Program, under the provisions of the program.

Objectives for 1977: No funds are provided in the 1977 President's budget for this program because other biomedical and behavioral research activities have a higher priority at this time.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Minority Biomedical Support

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$7,610,000	Indefinite	--	$7,783,000

Purpose: The Minority Biomedical Support (MBS) Program objectives are to increase the numbers of ethnic minority faculty, students, and investigators engaged in biomedical research. This can be accomplished by broadening the opportunities for participation in biomedical research, of ethnic minority faculty and student investigators, and by providing an appropriate setting in which these goals can be accomplished. The MBS Program is the major focus and effort of the NIH to involve minorities in biomedical research. The authorizing legislation is Public Health Service Act, Title III, Part A.

Explanation: The MBS Program was started in 1972 at the encouragement of the Congress. Since its initiation, the MBS Program has been expanded and modified. Some institutions now eligible include two-year colleges, and colleges and universities having a large number of ethnic minority students, in addition to the traditional ethnic minority colleges, universities and health professional schools.

Applications for grant awards are submitted by institutions to the Minority Biomedical Support Program. The applications are reviewed by the General Research Support Program Advisory Committee and the National Advisory Research Resources Council. 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 and no indirect costs are allowable.

Accomplishments in 1976: An estimated 75 grants supporting 80 minority institutions will be awarded in 1976. Grantees include 58 schools with a predominance of Blacks, 17 schools with a predominance of Spanish-speaking students, 3 schools with a large number of American Indians, and 2 schools with a large number of Hawaiian/ Polynesian students. Six-hundred faculty and 1,300 students will be supported from the MBS Program.

Program Plans for 1977: With the total funds requested for 1977, continued support will be provided to an estimated 75 grants for institutional research programs involving minority scientists in biomedical research and exposure of minority students to the challenges and opportunities of biomedical research.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Chemical/Biological Information-Handling Research

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
--	$1,000,000	Indefinite	--	$1,092,000

Purpose: The Chemical/Biological Information-Handling Research (CBIHR) Program develops new computer-based tools for handling research information about chemical substances and their biological effects. The authorizing legislation is Public Health Service Act, Title III, Part A.

Explanation: The CBIHR Program makes contract awards. This unique research resource is called PROPHET. It is the most comprehensive array of computer tools for research on chemical/biological interactions ever integrated into a single system. PROPHET is a national shared resource. Its services are allocated competitively via a peer review process with the users helping to defray the operating costs of the System with funds from their own research grants and contracts. Scientists are able to deal with larger amounts of complicated types of data and conduct experiments that would be impossible without these advanced computer tools.

Accomplishments in 1976: The CBIHR Program has (a) enlarged the community of PROPHET users to over 100 scientists at 12 sites in 9 states; (b) made possible the creation of a unique computer data bank containing the latest research information on the three-dimensional shapes of chemical substances known to affect fertility, child development, and a host of other life processes; (c) facilitated research on a wide variety of medical problems such as how diseased kidneys handle drugs and other blood constituents, how alcohol and other drugs affect the brain, and how the body is able to react selectively against specific foreign chemical substances as in the case of an allergic response or the rejection of a transplanted organ; and (d) continued to have PROPHET users share in the operating costs of the System at approximately $6,000 per user group per year. In 1976, two contracts were issued.

Objectives for 1977: The CBIHR Program will (a) expand the community of PROPHET users to approximately 125 scientists at 15 sites; (b) make possible the continuing development and broad dissemination of a unique data bank on the chemical structure of the specialized proteins which are a key component of the body's immunity against foreign substances; (c) facilitate new investigations of a wide variety of clinically important chemical substances such as those which are involved in the regulation of blood pressure, those which affect the body's basic metabolic rate, and those which destroy or retard the growth of cancer cells; and (d) increase to approximately $10,000 per user group per year the extent to which PROPHET users share in the operating costs of the System. In 1977, two contracts will be issued.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Direct Operations

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
60	$2,525,000	Indefinite	57	$2,670,000

Purpose: The Division's special programs of resource and center grants, fellowships and research contracts are administered by this activity.

Explanation: This activity supports the Division of Research Resources' extramural program staff which administers and manages the research resource grants and contracts, plus the formula grants of the Biomedical Research Support Programs. There are no matching requirements. The Programs' staff are responsible for the planning and development of their programs which will best serve the Program's mission and the health mission of NIH. They review and evaluate the grant applications for presentation to the National Advisory Research Resources Council. They also provide assistance and act as liaison with applicants and grantees, and provide continuing surveillance of the grants. Scientific and technical review of each of the grants is also provided to assure that the scientific mission of the Programs are fulfilled. Authority is Public Health Service Act, Title III, Part A.

Accomplishments and Objectives in 1976 and 1977: This activity will continue to administer, manage, and review the grants and contracts. Planning, development, and scientific review will be continued to assure that the Programs will contribute to promote NIH's health mission.

A total of 766 awards are expected to be issued in 1976 and 317 awards are estimated to be issued in 1977. No funds were requested in 1977 budget for the Biomedical Research Support Program and has caused a decrease of 407 grants in 1977. There are 190 site visits planned each year to new applicants and to current awardees.

Several workshops are to be arranged nationally for the advance study of sophisticated technologies and their applications to the advancement of biomedical science.

The staff will attend and participate in several national society meetings and will also sponsor a symposium for the Division's Minority Biomedical Support Program at Xavier University in New Orleans at which an expected 270 papers on biomedical sciences are to be presented. Two Directors meetings are planned for 1976 so that the directors who administer the grants which they receive from NIH will be able to discuss their joint problems together and will also allow the Programs to explain, train, and elucidate their goals and policies.

The Division's staff will continue its active participation in the Inter-Agency Primate Steering Committee which is developing plans for the provision of adequate primate supplies for both the NIH's extramural and intramural research efforts.

NATIONAL INSTITUTES OF HEALTH

Research Resources

Program Purpose and Accomplishments

Activity: Program Management

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
17	$592,000	Indefinite	17	$627,000

Purpose: This activity provides the general administration, planning, direction, and coordination of the Division's programs.

Explanation: Program Management funds the Office of the Director and related staff and includes the Office of Science and Health Reports. The six programs which they administer are Clinical Research, Biotechnology Research, Laboratory Animal Sciences and Primate Research, Biomedical Research Support, Minority Biomedical Support, and Chemical/Biological Information-Handling Research.

Accomplishments in 1976: The Division continued its "interfacing" meetings with the officials of the categorical Institutes to diffuse information about the types and capabilities of ongoing Division-supported resources. In addition, the Division acquired information about the current needs and the future plans of the Institutes. This increased interaction will assure the Division's Programs are responsive to the needs of the investigators supported by NIH and will also aid in the forward planning of new resource development activities.

Objectives for 1977: This activity will continue to provide the overall direction, management, administration, and coordination of the Division's Programs.

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Estimate	Transition Quarter
1. Clinical Research	42,619,000	8,550,000
2. Biotechnology Research	12,153,000	7,068,000
3. Laboratory Animal Sciences and Primate Research	20,844,000	1,237,000
4. Biomedical Research Support	42,957,000	
5. Minority Biomedical Support	7,610,000	1,705,000
6. Chemical Biological Information Handling Research	1,000,000	900,000
7. Direct Operations	2,525,000	652,000
8. Program Management	592,000	153,000
Total	130,300,000	20,265,000

Funds are requested for the transition quarter to provide support to those continuation grants and contracts with anniversary dates in the transition quarter and for supplemental awards to change those grants with anniversary dates of October 1 and November 1, 1976 to December 1, 1976.

TUESDAY, MARCH 2, 1976.

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDIES IN THE HEALTH SCIENCES

WITNESSES

DR. MILO D. LEAVITT, JR., DIRECTOR
DR. DONALD S. FREDRICKSON, 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
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, BUDGET

Mr. NATCHER. The committee will come to order.

At this time, we take up the John E. Fogarty International Center.

We have before the committee Dr. Milo Leavitt, the Director. Who do you have with you Dr. Leavitt.

Dr. LEAVITT. Mr. George Presson, my Executive Director.

Mr. NATCHER. Doctor, if it meets with your approval, we would like to insert your statement in the record as though you have read it. We will also include at this point your biographical sketch.

Dr. LEAVITT. Fine.

[The material 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, Wisconsin.

Education: 1933–1938—University of Wisconsin, B.A. 1938–1940—University of Pennsylvania, M.D. 1945–1948—University of Minnesota, M. Sci. 1958–1959—Harvard University, M.P.H.

Experience:

1968 to present—Director, John E. Fogarty International Center for Advanced Study in the Health Sciences, NIH.

1972 to 1974—Member, U.S. Delegation to 25th, 26th and 27th World Health Assemblies, Geneva.

1967 to 1968—Acting Director, Office of Program Planning, NIH.

1967—Deputy Director, Office of Program Planning, NIH.

1966 to 1967—Deputy Assistant Secretary for Science and Population, DHEW.

1966—Science Policy Coordinator, OS–ASH, DHEW.

1962 to 1966—Head, Special International Programs Section, Office of International Research, NIH.

1960 to 1962—Assistant Chief, Perinatal Research Branch, National Institute of Neurological Diseases and Blindness, NIH.

1959 to 1960—Chief, Project Services Branch, Collaborative Research, NINDB, NIH.

1958 to 1959—Postdoctoral Public Health Trainee, Harvard School of Public Health, Boston, Massachusetts.

1949 to 1958—Clinical Assistant Professor Medicine, Medical College of Pennsylvania, Philadelphia, Pennsylvania.

1945 to 1949—Fellow, Internal Medicine, Mayo Clinic, Rochester, Minnesota.

1942 to 1945—Captain, U.S. Army Medical Corps.

1940 to 1942—Rotating Internship, Philadelphia General Hospital, Philadelphia, Pennsylvania.

Association memberships: 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 Association; Alumni Association of the Mayo Foundation; American Public Health Association; Fellow, College of Physicians of Philadelphia.

GENERAL STATEMENT

Mr. Chairman and members of the committee, I am pleased to have this opportunity to appear before you and to present the programs of the Fogarty International Center.

SENIOR INTERNATIONAL FELLOWSHIPS

One of the most rewarding areas of international activities is the opportunity to increase biomedical knowledge through successful exchange programs. In fiscal 1975, we announced the establishment of a fellowship program designed to provide opportunities to faculty members of U.S. schools of medicine, osteopathy, dentistry and public health to go abroad to study and share their expertise. From the early initiation of this program, the response of faculty members of those schools has been enthusiastic. With few exceptions, applications for these fellowships are of such high quality that each could merit an award. In the initial period 29 of 36 applications were funded. In fiscal 1976, 33 fellowships have been awarded. There is no doubt that as news of this program is further disseminated applications to engage in this valuable exchange will increase. Our request today provides for an increase of 25 senior international fellowships.

INTERNATIONAL RESEARCH FELLOWSHIPS

Another fellowship program of longstanding interest in the United States and abroad is the International Research Fellowship program which provides opportunities to selected young foreign research scientists to engage in research study and collaboration with U.S. scientists in leading U.S. universities and institutions. Working with and through national committees of the approximately forty participating countries, applications of the most competent young scientists of each of these countries are reviewed in competition for scientific merit and a limited number are awarded.

This program has had a profound effect upon research both in the United States and abroad. We have received many unsolicited laudatory comments from American scientists about the value of this program as a research stimulus in the United States as well as its influence in research and research management abroad. During the history of this program, over 1,500 fellowships have been awarded. However, in recent years, because of reduced financial resources and increases in stipend the number of awards has been decreasing. We are pleased therefore to be able to include in our request this year sufficient funds to not only restore this program to its former level but to increase the number of awards to each country as well as the possible addition of other countries with whom the United States has negotiated formal bilateral agreements.

FOGARTY SCHOLARS-IN-RESIDENCE

This program has had 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 biomedical disciplines to the Center to pursue their scholarly interests and contribute to the academic interests of the Institutes of the National Institutes of Health. Unique opportunities for furthering scientific work and exchange prevail, not the least of which is the opportunity for groups of these outstanding scientists of varied disciplines to collectively consider current health problems. The scholars have also become involved in the immediate interests of the respective Institutes, as well as many U.S. universities and Institutions. For example:

Dr. Elvin A. Kabat, an immunochemist from Columbia University, came to the Fogarty Center in the spring of 1974 as a scholar-in-residence. During his year's residence he completed the second edition of his book on "Structural Con-

cepts in Immunology and Immunochemistry" which is a standard text in the field. Dr. Kabat also published several important papers on the structure of immunoglobulins in the Proceedings of the National Academy of Sciences in collaboration with one of the staff of NIAMDD. The chemistry of immunoglobulins is fundamental to the study of immunity to infectious diseases. Dr. Kabat stimulated a number of conferences and seminars during his year at NIH. As a result of his scholarship and the relationships developed with several of the institutes he has become a regular collaborator with NCI scientists studying the role of immune mechanisms in resistance to cancer. His presence on the campus during 1974–75 was invaluable to many laboratories in several institutes in NIAMDD, NIAID, and NCI.

Dr. Gordon Hammes, chairman of the chemistry department at Cornell University, is currently a scholar-in-residence. Dr. Hammes is a leading structural chemist who is today working on the nature of cell surfaces. During his stay, he is collaborating with scientists in NCI and NIAMDD who are working on cell membranes and how they regulate metabolic processes in health and disease. He has organized a conference on the subject which will take place at the Fogarty Center in May 1976 to which a number of leading researchers have been invited. This meeting will be an important contribution to understanding the role of biological membranes in controlling the growth of neoplastic or cancerous tissues.

ADVANCED STUDY

The objectives of this program are:

(1) To promote advanced study in the health sciences through international conferences, seminars and workshops on subjects and research areas falling within the scope of the NIH mission;

(2) To identify the legal, ethical, social and economic problems that may arise from continuing biomedical research and to advance our understanding and insight into these problems; and

(3) To stimulate research concepts in specific fields through interaction among the international and national biomedical research community.

I am keenly aware of the strong interactions between the programs of the Center and the interests and responsibilities of the National Institutes of Health, as well as other Federal agencies. Our efforts therefore, are carefully coordinated with these other agencies and are intended to complement existing capabilities through cooperative effort.

In support of the biomedical research mission of the National Institutes of Health, we have concentrated our efforts in the last year in two areas which interrelate—the immune system and the biology of cell surfaces. Research in these areas holds great promise for the prevention of cancer and immune deficiency diseases. The Fogarty Center has sponsored recent conferences on the function of cell surfaces in malignant development, modulation of host resistance to induced neoplasia, and immunologic control of virus-associated tumors.

Encouraged by the Institutes and other Public Health Service agencies, we have participated with the Association of Teachers of Preventive Medicine and the American College of Preventive Medicine in supporting task force studies within eight areas. Their findings and recommendations were used in preparing the "prevention theme" of the Department's "Forward Plan for Health" and are being considered by Public Health Service agencies for appropriate implementation in their programs. In this connection, we have just received a copy of the report of the National Commission on Diabetes wherein they recommend the convening of interdisciplinary workshops, symposia, and conferences to encourage cross-fertilization of ideas and cooperative research efforts. They further recommend that the Fogarty International Center, among others, have as part of its charge the sponsorship of such meetings. They also suggested that, in view of the fact that very important research is conducted in many countries throughout the world, these proposed meetings should include appropriate scientists from other countries to share their ideas.

We believe that our experiences in utilizing the talents, knowledge and skills of overseas investigators in examining health and biomedical research and the promotion of international cooperation will be most beneficial to the implementation of those recommendations.

In addition to Fogarty Center inititatives, we are working with the Institutes in developing conferences and workshops of multi-Institute interest.

As we have reported previously, we are engaged in a continuing series of comparative studies of health and biomedical research abroad. In view of the widespread interest of this country in the U.S.S.R. and the People's Republic of China, a number of our first studies were devoted to those areas. We have not limited our interest, however, solely to them. For example, one of the Fogarty scholars, Sir George Godber, delivered a series of lectures on the British National Health Service to a number of NIH and other Federal agency administrators and, at the present time, we are preparing for a series of conferences in cooperation with the Royal Society of Medicine of the United Kingdom to discuss mutual problems of biomedical and health research. In addition, we are continuing our studies of the Western democracies, considering such areas as planning, regulation, supply and demand for services and priority determination. Their experiences may provide valuable information to us as we seek to improve our own system.

HEALTH POLICY STUDIES

The Center established a Health Policy Studies program designed to examine multidisciplinary interrelationships of health systems, utilizing the Intergovernmental Personnel Act to convene a group of visiting professors from U.S. universities to serve as directors for such studies. Topics of study interest to the group are Federal-subnational relations in health planning and regulation, the doctor-patient relationship in the changing health scene, alternative policies for containing health costs and surgical-hospital utilization policies to improve quality control. The results of such studies, which involve physicians, health economists, medical sociologists and political scientists should provide a better knowledge of how other countries' policies might be employed to provide a better insight into the U.S. system and propose various means of dealing with our problems.

ADMINISTRATIVE SUPPORT

Although we have not in the past, spoken about the administrative support functions of the Center, which utilize almost one-half of our total staff, as a result of recent discussions with the Director, National Institutes of Health, the role of the Center as a focus, information and coordination point for all international activities at NIH has been clarified. Thus, the Center's knowledge about international activities, foreign scientists, health officials and policies will be better utilized to provide staff support to the Director, NIH and the individual institutes.

For these programs and activities, the Fogarty International Center is requesting $7,492,000. I shall be pleased to reply to any questions of the committee.

INCREASED FUNDING

Mr. NATCHER. Although the dollar increases in the budget are not substantial compared to most of our accounts, the percentage increase requested here is one of the largest. Could you tell this committee generally why the increase is necessary.

Dr. LEAVITT. The increase will restore the program to the 1972 level, while, at the same time, projecting the increased cost of fellowship awards.

GORGAS MEMORIAL INSTITUTE

Mr. NATCHER. Why are you funding the Gorgas Memorial Institute at a level of $500,000 when the Congress raised the level to $860,000?

Dr. FREDRICKSON. Mr. Natcher, $500,000 has been the level of support for the Gorgas Laboratory in recent years.

This budget you have before you was prepared and submitted before the 1976 appropriation became law. For 1976, the Congress not only made $860,000 available in the Fogerty Center appropriation but directed us, in the Conference Report on the Bill, to make an addi-

tional $500,000 available from the Allergy Institute's appropriation. Gorgas will thus have a total of $1.3 million in fiscal year 1976.

Mr. NATCHER. Last year we talked about your establishing a more formal relationship with the Gorgas Center. Have you developed a formal plan?

Dr. FREDRICKSON. We have recently had conversations with the Gorgas Memorial Institute, Mr. Natcher, and we have developed a plan for a better overview. This will provide the NIH with an opportunity to review, annually, the scientific capability and activities of the Gorgas Institute. We hope to implement that within the coming year.

Mr. NATCHER. Is the Gorgas Memorial Institute eligible for grants from the other NIH institutes and how well have they done insofar as competition for grants is concerned?

Dr. FREDRICKSON. They are indeed eligible for grants and contracts from any of the other institutes and they have had support from the Allergy Institute in the past several years. I would have to submit for the record a complete compilation of the grants but the support amounted to something in the area of $500,000.

Mr. NATCHER. Have they done well or maybe they have not done too well, Dr. Fredrickson, which is it?

Dr. FREDRICKSON. I think they do first-rate research. They have problems in recruiting and retaining certain scientific personnel, which they need for the strongest program. But they are competitive and are capable of doing important and useful work in this important area.

Mr. NATCHER. Dr. Leavitt, since a substantial part of the research work conducted by the Gorgas Institute would also benefit the Latin American countries, has the Pan American Health Organization provided any support that you know of?

Dr. LEAVITT. They have provided modest support and it is my understanding that this support will be continued next year.

Mr. NATCHER. If you will list the total operating budget for 1974, 1975, 1976, and 1977 and identify the sources of support.

Dr. LEAVITT. We would be pleased to do that.

[The information follows:]

GORGAS MEMORIAL INSTITUTE OF TROPICAL
AND PREVENTIVE MEDICINE, INCORPORATED

OPERATING BUDGET (IN THOUSANDS OF DOLLARS)
FOR FISCAL YEARS 1974, 1975, 1976 and 1977

		1974 Actual	1975 Actual	1976 Estimate	1977 Estimate
REVENUES					
U.S. Government Contribution:					
FIC		$500	$500	$860	$500
NIAID		--	208	500	--
TOTAL		$500	$708	$1,360	$500
Research Grants & Contracts:					
National Institutes of Health					
NIAID-2514	MARU	657	729	--	--
NIAID-01251	Leishmaniasis	154	56	--	--
NIAID-02984	Ecology	125	116	120	--
NIAID-11889	Microclimate	6	28	20	5
	Total NIAID	$942	$929	$140	$5
Division of Research Resources					
RR05769	General Research Support	--	--	38	--
	TOTAL NIH	$942	$929	$178	$5
U.S. ARMY					
C-0032	Training	$7	--	--	--
C-2031	Monkey Hosts	91	$82	$30	--
C-3017	MARU	99	99	119	--
C-8137	Pond Stabilization	38	5	--	--
G-9406	Blackfly	--	37	56	--
	TOTAL ARMY	$235	$223	$205	--
U.S. NAVY					
C-0108	Chagas Immunity	$13	$10	$4	--
C-1580	Training	25	25	25	--
	TOTAL NAVY	$38	$35	$29	--
Agency for International Development		$23	$120	--	--
New England Regional Primate Research Center		1	5	$5	$4
Pan American Health Organization		--	8	4	--
Smith, Kline & French Laboratories		--	2	--	--
TOTAL GRANTS AND CONTRACTS		$1,239	$1,322	$421	$9
Other Miscellaneous Income		5	3	3	3
TOTAL REVENUES		$1,744	$2,033	$1,784	$512

NOTE: The above table was submitted by the Gorgas Memorial Institute and the method of presentation does not conform to the actual fiscal year funding by NIH. From the 1975 Appropriation, FIC and NIAID each obligated $500,000 for the general support of Gorgas. The $500,000 for NIAID in 1975 was split between the item U.S. Government contribution ($208,000) and MARU ($292,000).

GORGAS MEMORIAL INSTITUTE OF TROPICAL
AND PREVENTIVE MEDICINE, INCORPORATED

OPERATING BUDGET (IN THOUSANDS OF DOLLARS)
FOR FISCAL YEARS 1974, 1975, 1976 and 1977
(continued)

	1974 ACTUAL	1975 ACTUAL	1976 ESTIMATE	1977 ESTIMATE
OPERATING EXPENDITURES:				
Direct Research				
1. Biomedical Educational Resources Center				
Medical Library	$ 34	$ 36	$ 35	$ 36
Computer Center	-	-	5	28
Educational Center	7	11	1	6
	$ 41	$ 47	$ 41	$ 70
2. Primate Center				
Reproductive Studies	$ 1	$ 5	$ 7	$ 8
Simian Diseases	-	-	5	5
Experimental Models	154	161	97	84
	$ 155	$ 166	$ 109	$ 97
3. Division of Infectious Diseases				
Bacterial Diseases	$ 62	$ 60	$ 59	$ 62
Parasitic Diseases	219	204	95	105
Virus Diseases	453	533	225	208
Zoonosis	27	7	20	25
	$ 761	$ 804	$ 399	$ 400
4. Division of Ecology & Epidemiology				
Ecology	$ 185	$ 153	$ 152	$ 151
Epidemiology	4	13	27	35
Experimental Biology	35	19	20	26
	$ 224	$ 185	$ 199	$ 212
5. Division of Clinical Investigations				
Immunopathology	$ 104	$ 93	$ 75	$ 78
Clinical Services	-	17	25	31
	$ 104	$ 110	$ 100	$ 109
6. Administration				
Washington, D.C.	$ 73	$ 75	$ 86	$ 86
Panama & Canal Zone	229	282	161	125
Reserve for Termination & Repatriation	-	22	100	100
	$ 302	$ 379	$ 347	$ 311
7. Plant & Equipment Maintenance				
Gorgas Memorial Laboratory - Panama	$ 114	$ 115	$ 113	$ 142
Plant Renovation	-	-	150	-
Building 265 - Canal Zone	181	231	170	171
	$ 295	$ 346	$ 433	$ 313
TOTAL EXPENDITURES	$1,882	$2,037	$1,628	$1,512
EXCESS (DEFICIENCY) OF REVENUES OVER EXPENDITURES	$ (138)	$ (4)	$ 156	($1,000)

Mr. NATCHER. Doctor, how can we provide a more stable level of support for the Gorgas Institute?

Dr. FREDRICKSON. I believe, Mr. Natcher, that it is important to integrate the several sources of core support they have had from both the Fogarty Center and the Allergy Institute into one place. We recommend that the Fogarty Center be the focal point. That would be on the basis of an annual review. They would certainly be permitted then to supplement that by applying for grants or contracts, under the usual review mechanism, from the Allergy or any other institute.

SCHOLARS PROGRAM

Mr. NATCHER. Now, let me direct your attention to the scholars program where the distribution of funds to your various activities is not too clear to the committee. Could you explain the number of awards expected to be made under each program and the portion of the $3.7 million which will go to each?

Dr. LEAVITT. The Fogarty scholars-in-residence program which is a small one, involves eight awards to outstanding authorities from the United States and throughout the world. That accounts for an amount of $270,000 a year. This represents but 7 percent of the fellowship budget. Our international fellowships are awards made to outstanding young scientists from abroad who come to the United States for a period of a year or a year and a half of research training. In the 1977 President's budget we would be able to award 170 such awards which is an increase of 93. This increase would permit us to restore the international research fellowship program to the 1972 level. The request for this program is $2,380,000 or 65 percent of the fellowship budget.

The senior fellowship program, the third of our programs, is a program which permits faculty members at midcareer in U.S. schools of medicine, osteopathy, dentistry, and public health to go abroad and share their expertise. The cost of this program, representing 28 percent of the fellowship budget is $1,050,000.

Mr. NATCHER. I believe during fiscal year 1976 you proposed to double the awards. This number then would be what? 236.

Dr. LEAVITT. Yes.

Mr. NATCHER. Is this a part of a long-range plan? Is that what you have in mind?

Dr. LEAVITT. Yes; the total increase of 236 scholars represents several efforts. The international research fellowship program has been in existence since 1958 and has had a very beneficial effect upon research in the United States and research and research management abroad. Unfortunately, this program has been decreasing since 1972 and our request supports the effort to restore these fellowships to the 1972 level while at the same time projecting the increased costs per award.

The senior international fellowship program is a relatively new program, having been initiated in 1974. Our request reflects the increased interest in the program.

Mr. NATCHER. Dr. Leavitt, what is the procedure for publicizing these awards and what are the selection criteria?

Dr. LEAVITT. For each of the programs, sir?

Mr. NATCHER. Yes.

Dr. LEAVITT. The Fogarty scholars in-residence are selected by an in-house group of senior sicentists at NIH. The Fogarty scholars, who

may either be U.S. scientists or from abroad, are selected on the basis of their reputation and the kinds of talent and expertise they can bring to the NIH scene because we expect the scholars to involve themselves in the biomedical community. They conduct seminars for our younger scientists; organize international conferences in fields of their expertise; and provide consultation, guidance, and offer suggestions to the research scientists at NIH.

The international fellowship program consists of younger people who are about 5 years postdoctoral. They are selected initially by a national nominating committee from their own country, of which there are about 40. They review perhaps 10 or 12 and select 3 or 4 of these persons to enter into the final competition conducted at NIH. The applications are reviewed by a special group of NIH intramural scientists for scientific merit. It is our observation that these young promising foreign scientists bring an unusual knowledge and experience to American laboratories. The senior international fellowships were developed initially in response to a longfelt need for U.S. health professionals at midcareer to study abroad, yet, at the same time exchanging experiences and sharing their expertise among foreign laboratories and institutions. Applications from faculty members of U.S. schools of medicine, osteopathy, dentistry, and public health are reviewed by a special study section. If approved, we provide a modest stipend, transportation, and a small sum to support their activities in the host institution abroad.

This provides a two-way street, an exchange program in the real sense of the word in that we are gaining the knowledge and expertise and new ideas from the younger men coming under the international research fellowship program and we are exporting some of our expertise abroad.

ADVANCED STUDIES

Mr. NATCHER. Doctor, in your budget justification, you support advanced studies in preventive medicine, health care delivery, and environmental health. I wish you would give the committee a brief explanation of the work you are conducting in these areas.

Dr. LEAVITT. Several years ago, we believed at NIH that a new look should be taken at what could be accomplished in prevention. We convened a group of representatives from NIH, other agencies within the Public Health Service, and the public sector to determine what areas needed to be studied and would be most fruitful in terms of prevention. A number of areas such as diseases of fetal and perinatal development, diabetes, and obesity were proposed. This became a part of the forward plan for health of the Assistant Secretary for Health in HEW.

We considered the possibility of further work in cancer and heart and lung, however, both the National Cancer Institute and the National Heart and Lung Institute had already made a sizable investment in this area so we did not engage in those two particular areas of disease.

We convened groups of specialists who provided us with state-of-the-art reviews in a variety of subjects. Among the first of these was the problem of oral health, which was accomplished in close cooperation with the National Institute of Dental Research. This resulted in a monograph which was published.

We also considered the problem of obesity, which we considered of public health importance in this country. In this subject, as well as all the preventive health studies, we established a task force of specialists in this area, who utilized the talents of many more experts and produced a two-volume state-of-the-art review. We did the same thing on the subject of diabetes mellitus before there was a National Commission on Diabetes. Our papers and manuscripts on diabetes were submitted to the National Commission for their use. We continuted our work with the American College of Preventive Medicine, the Association of Teachers of Preventive Medicine, and the Deans of Schools of Preventive Medicine to determine what needed to be done in the way of additional research in some of these areas and in June of 1975, the Fogarty Center sponsored a National Conference on Preventive Medicine from which a series of recommendations were developed. These are now being further examined.

In all cases, we have worked closely with our sister institutes and agencies within the Public Health Service.

We are culminating most of our work in preventative medicine during this coming year. We shortly will be having meetings and conferences on renal disease working closely with the National Institute of Arthritis and Metabolic Diseases.

At the very start of our program on preventive medicine, the Association of Teachers of Preventive Medicine requested our assistance in developing an improved curriculum in preventive medicine. Utilizing the assistance of the Association, the Institutes of NIH and other agencies within the Public Health Service, we have developed eight monographs devoted to the improved teaching of preventive medicine. These monographs are: "New Health Practitioners"; "Teaching of Chronic Childhood Illness and Aging"; "Chronic Childhood Illness: Assessment of Outcome"; "The Behavioral Sciences and Preventive Medicine: Opportunities and Dilemmas"; "Preventive/Community Medicine in Primary Care"; "Consumer Participation in Health Care"; "Academic Relationships and Teaching Resources"; and "Toward an Educated Health Consumer."

A number of other publications relating to the state of the art of preventive medicine have been published or are in preparation. Upon the completion of these documents, most of our work in preventive medicine will terminate.

Environmental health was your second area.

ENVIRONMENTAL HEALTH

We have worked very closely, particularly during the early years of the Fogarty Center, with environmental scientists focusing on heavy metal contamination in human health, environmental factors in respiratory disease, and the mutagenic effects of environmental contaminants. Publications on these subjects were utilized at the Stockholm Conference on the Environment in 1972. We worked closely with Dr. Rall and his associates at the National Institute of Environmental Health Sciences.

Mr. NATCHER. I think that pretty well covers it. When you get the record back you can amplify anything you might want to add to it.

Dr. FREDRICKSON. May I add a comment?

Mr. NATCHER. Go ahead.

Dr. FREDRICKSON. Since coming on as Director of NIH, I have been evaluating, among other aspects, our commitments to the international health scene. I have been particularly concerned how this problem continues to increase and how important has been the contribution of the Fogarty Center in permitting the Institutes to carry out a number of ascending activities abroad. I think international health and research is extremely helpful to us so we can retain parity and, of course, it is our intent to attain nothing less than supremacy throughout the year and our need to interact with scientists increases.

The director of Fogarty Center and I have reviewed the priorities of the Fogarty Institute and have made some adjustments in the priority of those activities toward those activities which relate to the interface of the institutes. We have summarized some of that intent in a report to the Senate Appropriations Committee. If you have not received a copy we will be very glad to supply you with a statement as to our thoughts in this regard.

Mr. NATCHER. Do the other agencies of the Public Health Service have an interest in the areas you have just mentioned? Do they participate or do they act as advisers?

Dr. LEAVITT. They act both as advisers and participants. We rely upon the advice and technical expertise provided to us by agencies within the Public Health Service. We are eager, for example, that the work we have undertaken in preventive medicine, particularly in consumer health education involve our colleagues at the CDC Bureau of Health Education which has recently been established, but is not fully operational at this point.

Mr. NATCHER. List the agencies which participated and the role they played in the advanced studies program.

Dr. LEAVITT. All right.

[The information follows:]

FOGARTY INTERNATIONAL CENTER

Advanced Study Program

Studies	Other Agency or Institute Participation	Nature of Participation
Advisory Committee, National Conference on Preventive Medicine	American College of Preventive Medicine	Cosponsor
	Bureau of Health Manpower	Participant
	Center for Disease Control	Participant
Academic Missions of Departments of Preventive Medicine	American Academy of Family Physicians	Participant
	Association of American Medical Colleges	Consultant
Pan American Child Health Planning Meeting	Pan American Community Health Association	Participant
	American College of Preventive Medicine	Participant
	National Institute of Child Health and Human Development	Participant
Expert Panel on Education and Training of Physicians in Preventive Medicine	American College of Preventive Medicine	Participant
	Bureau of Health Manpower	Participant
	Office of Policy Development and Planning, Office of the Assistant Secretary for Health, DHEW	Participant
	American Association of Colleges of Pharmacy	Participant
	Senator Cranston's Legislative Assistant	Consultant
Conference on the Atmosphere: Endangered and Endangering	National Institute of Environmental Health Sciences	Co-host
	Energy Research and Development Administration	Participant
	National Bureau of Standards	Participant
	National Center for Atmospheric Research	Participant
	National Center for Atmospheric Research	Participant
	National Academy of Sciences	Participant
Conference on Cellular Regulation of Transport and Uptake of Nutrients	National Institute of Neurological and Communicative Disorders and Stroke	Participant
	National Institute of Arthritis, Metabolism and Digestive Diseases	Participant
	National Cancer Institute	Participant
	National Heart and Lung Institute	Participant
	National Institute of Aging	Observer
	National Institute of Mental Health	Observer
	National Institute of General Medical Sciences	Observer

Expert Panel on Consumer Health Education in Preventive Medicine	American College of Preventive Medicine	Participant
	National Institute of Aging	Participant
	Office of Policy Development and Planning, Office of the Assistant Secretary for Health, DHEW	Participant
	Bureau of Health Manpower	Participant
	National Institute of Child Health and Human Development	Participant
	National Cancer Institute	Participant
	Food and Drug Administration	Participant
	National Institute of Dental Research	Participant
	National Institute of Arthritis, Metabolism and Digestive Diseases	Participant
	Center for Disease Control	Participant
	National Heart and Lung Institute	Participant
International Symposium on Idiopathic Urinary Bladder Stone Disease	The Eastern Mediterranean Regional Office, World Health Organization	Cosponsor
	National Institute of Arthritis, Metabolism and Digestive Diseases	Participant
Symposium on Ocular and Cerebrospinal Fluids	National Eye Institute	Participant
	National Institute of Neurological and Communicative Disorders and Stroke	Participant
	National Cancer Institute	Participant
	Armed Forces Radiobiology Research Institute	Participant
	Naval Medical Center	Participant
International Health Costs and Expenditures	Health Resources Administration	Participant
	Health Services Administration	Participant
	Office of the Assistant Secretary for Health, DHEW	Participant
Community Medicine in England and Scotland	Health Resources Administration	Participant
Federal/State Relationships in Health	Health Resources Administration	Participant
	Health Services Administration	Participant
	Office of the Assistant Secretary for Health, DHEW	Participant
The Doctor/Patient Relationship in the Changing Health Scene	Health Resources Administration	Participant
	Health Services Administration	Participant
	Office of the Assistant Secretary for Health, DHEW	Participant
Policies for the Containment of Health Care Costs and Expenditures	Health Resources Administration	Participant
	Health Services Administration	Participant
	Office of the Assistant Secretary for Health, DHEW	Participant

Canadian National Health Insurance	Health Resources Administration	Participant
	Health Services Administration	Participant
	Office of the Assistant Secretary for Health, DHEW	Participant

FOREIGN CURRENCY

Mr. NATCHER. I know the Center over the years has made use of foreign currency accounts. Can you tell us how much benefit these funds have been in your work?

Dr. LEAVITT. Our present expenditure of foreign currencies amounts to a little over $1.5 million a year. This level may fluctuate from time to time. With experience gained since 1962, we now realize there is much to be learned from working in collaboration with our scientific colleagues in India, Pakistan, Egypt, and elsewhere.

We have also been pleased with the results of our investment in scientific endeavors in Israel, particularly in the fields of biochemistry, immunology and cardiovascular diseases. This was followed by a heightened interest in Poland where a number of projects were developed, particularly in the neurosciences, microbiology, and cancer. We then explored opportunities in Yugoslavia where we found much interest in neuropathology, and industrial health.

These foreign currencies have provided a unique opportunity to utilize the expertise, the unique populations or unusual disease patterns which may be found abroad but are not available in the United States. For a variety of reasons a very good research program has evolved.

GORGAS MEMORIAL LABORATORY

Mr. NATCHER. You mention funding the Gorgas Laboratory completely out of your budget. What amount did you have in mind and would we have to increase the Fogarty budget to do what you suggest?

Dr. FREDRICKSON. I think, Mr. Natcher, if we were to increase the support over what is in the current 1977 budget submission to you, we would take another look at the Fogarty budget, most specifically at the fellowship and scholarship programs, and try to adjust our priorities to see if we could live with a smaller increase there and from that allocation provide support for Gorgas up to the 1976 level, if possible.

GORGAS MEMORIAL INSTITUTE

Mr. NATCHER. Doctor, if the committee accepted your suggestion to fund the Gorgas Memorial Institute out of the 1977 Fogarty Center budget—would you have sufficient funds remaining to allow for some expansion of the scholars program?

Dr. LEAVITT. Yes, sir, we would. It would require a reduction of the program as presented in the estimate before you. The number of awards to be reduced will depend upon the specifics of the committee's requirements.

Mr. NATCHER. Mr. Michel?

SENIOR INTERNATIONAL FELLOWSHIPS

Mr. MICHEL. To which countries do our people receiving senior international fellowships go in the main?

Dr. LEAVITT. The needs of the senior international fellows are best resolved in the more scientifically advanced countries. These would include the United Kingdom, France, Western Europe, Japan, and Israel.

Mr. MICHEL. What specific gains do we as a nation achieve by having these people go abroad? Can you point to any specific accomplishments?

Dr. LEAVITT. Many foreign countries have much to offer in scientific research. And I think it safe to say that nearly all have far greater experience and knowledge in health care systems and health care delivery. In fact, although it is not conducted through this program, one of our principal interests in the advanced study program, is a series of comparative studies of health care and health care delivery systems, which may be of benefit to U.S. health planners. This program is in its first full year of operation and we do not have, at this time, reports of accomplishments from it.

Mr. MICHEL. What is the average dollar amount of the fellowship?

Dr. LEAVITT. The fellowship award is prorated at the rate of $18,000 per 12-month period. In addition, we provide transportation to the fellow only, as well as a modest amount to the host institution. Since some of these fellowships are not awarded for a full year, the average cost has been $16,000.

Mr. MICHEL. Why the almost doubling of this program in 1977? Is it that valuable.

Dr. LEAVITT. We have not done a very god job of advertising this program. Yet, almost immediately upon our first announcement, we received inquires from hundreds of faculty members and our first applications were so excellent that nearly all were awarded. During our most recent study section review, again nearly all were outstanding, but we are awarding only the very highest priority scores. Many excellent applications will go unfunded. We feel that with the experience of past fellows, the enthusiastic response to our first announcement, and with perhaps an improved announcement, that our request is not over optimistic.

INTERNATIONAL RESEARCH FELLOWSHIPS

Mr. MICHEL. How many international research fellowships are you planning to award in 1977, and what is average dollar amount per fellowship.

Dr. LEAVITT. We propose to fund 170 fellows at an average dollar amount of $14,000.

Mr. MICHEL. From which countries do most of the scientists come under this program?

Dr. LEAVITT. All applications from our participating countries are reviewed in competition by a study section and not all applications are approved. However, during the past 6 years, we have made awards to applicants from 31 countries. Thirteen countries, Sweden, Finland, Israel, Belgium, Japan, Spain, United Kingdom, Norway, Australia, France, Mexico, Chile, New Zealand, have received 21 or more awards and 9 other countries have received 10 or more awards.

Mr. MICHEL. What specific gains do we as a nation achieve from the program?

Dr. LEAVITT. Applicants for this program are selected by their nominating committees from the top young scientists in their country. These applicants are then reviewed in competition by an NIH study section. Thus, the awards are made to the very best young scientists abroad. They bring to our laboratories experience in problems and solutions achieved from working with unusual situations, health conditions and populations which are then brought to bear upon problems affecting the health of the American people. When these young scien-

tists return to their home country, they engage in collaborative studies with their American colleagues. A very great intangible benefit is also present, because these foreign scientists return to their home countries and achieve positions of responsibility where their roles in the battle of disease is of future benefit to the health of the American people.

STUDIES OF HEALTH SYSTEMS

Mr. MICHEL. How many studies do you have underway on the health systems abroad and health delivery systems in general?

Dr. LEAVITT. We are not supporting any studies of the total health systems of other countries. We are however, supporting studies which involve certain aspects of the health system. If I may, I would like to submit those for the record.

[The information follows:]

At the present time, we have eight studies on certain aspects of the health system, as follows: Utilization and Quality Controls under Canadian Health Insurance; the British National Health Service; the Danish National Health Insurance System; Health Planning in the U.S.S.R., the Doctor-Patient Relationship; A Comparison of International Views, Policies for Containing Health Costs; An International Perspective, National Subnational Relations in Health; an Analysis of the Implementation of the German Hospital Law of 1971; and an Analysis of the Implementation of French Policy on Health Insurance and Hospitals.

Mr. MICHEL. Don't such studies get into the policymaking field? How can we be certain that the findings of the studies won't be slanted to reflect the views of the researchers on the topic studied?

Dr. LEAVITT. The studies of foreign health experiences and attitudes are intended to provide new knowledge to individuals and institutions in the public and private sector concerned with the development of policies, designed to improve the health situation in the United States. When the studies have been completed the results are reviewed by referees with different views and backgrounds. The Center reserves the right to require any modifications necessary, in order to present the most objective point of view.

SCHOLARS IN RESIDENCE

Mr. MICHEL. How many scholars in residence are there, and what is the average cost per person?

Dr. LEAVITT. Our budget estimate is presented on the basis of an average stipend per man-year of $30,000. However, since the scholars are in residence for varying periods of time, the average cost per person is considerably less. The average cost per person during 1975 was approximately $13,000.

Mr. NATCHER. All right. We want to thank you and your associates for your time and effort.

JUSTIFICATION OF THE BUDGET ESTIMATES

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	1977 Estimate
Appropriation	$5,705,000	$7,492,000
Comparative transfers to:		
"Salaries and Expenses, State" CORE costs	-33,000	---
"Acquisitions, Operations and Maintenance of Buildings Abroad State" for CORE costs	-1,000	---
Comparative transfer from: "Office of the Director, NIH" to provide for standard level user charges	+23,000	---
Total obligations	5,694,000	7,492,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976-$200,000; 1977-$200,000.

John E. Fogarty International Center
for Advanced Study in the Health Sciences

Budget Mechanism

	1976 Number	1976 Amount	1977 Number	1977 Amount
Grants				
Special				
Gorgas Memorial Institute.....	1	$ 860,000	1	$500,000
Total Grants.....	1	860,000	1	500,000
Direct Operations				
Scholars.....	118	1,950,000	236	3,700,000
International Center.....	---	2,861,000	---	3,260,000
Standard Level User Charge....	---	23,000	---	32,000
Total.....	---	5,694,000	---	7,492,000

DHEW - National Institutes of Health

CROSSWALK - 1976 Column of 1977 Justification

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	$860	--	$860
2. Scholars.....		$1,950	1,950
3. International Center.....		2,884	2,884
Total Obligations.....	860	4,834	5,694

DHEW _ National Institutes of Health

CROSSWALK - 1977 Column of 1977 Justification

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		$3,700	3,700
3. International Center		3,292	3,292
Total Obligations	500	6,992	7,492

Summary and explanation of changes

1976 Estimated obligations	$5,694,000
1977 Estimated obligations	7,492,000
Net change	+1,798,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in				
1. Within-grade pay increases	---	$ 14,000	---	+$14,000
2. Increase per diem travel costs	---	49,000	---	+5,000
3. Federal Telecommunications System rate increases	---	20,000	---	+6,000
4. Service and supply rate increases.	---	70,000	---	+6,000
5. Annualization of pay increases	---	59,000	---	+17,000
6. Postage cost increase	---	31,000	---	+10,000
7. Program Evaluation and General Expense increases	---	117,000	---	+30,000
8. Payment to NIH Management Fund	---	233,000	---	+21,000
9. Payment to NIH Management Fund for SLUC	---	23,000	---	+9,000
Subtotal	---	---	---	+118,000
B. Program				
1. Scholars - to support 118 additional scholars	---	1,950,000	---	+1,750,000
2. International Center to support additional advance studies, including conferences, analyses of special subjects, and publication of the results	51	2,628,000	-1	+294,000
Subtotal	---	---	---	+2,044,000
Subtotal increases	---	---	---	+2,162,000
Decreases:				
A. Built-in				
One less day of pay	---	1,179,000	---	-4,000
B. Program				
Gorgas Memorial Institute - to continue programs at a level supported in 1975	---	660,000	---	-360,000
Subtotal decreases	---	---	---	-364,000
Total, net change	---	---	-1	+1,798,000

Obligations by Activity

Page Ref.		1976 Revised President's Budget Amount	Pos.	1976 Appropriation Amount	Pos.	1977 Estimate Amount	Pos.	Increase or Decrease Amount	Pos.
221	Gorgas Memorial Institute	$500,000		$860,000		$500,000		-$360,000	
222	Scholars	1,950,000		1,950,000		3,700,000		+1,750,000	
224	International Center	2,920,000		2,861,000		3,260,000		+399,000	
	Positions		51		51		50		-1
	Standard level user charge	23,000		23,000		32,000		+9,000	
	Total obligations	5,393,000		5,694,000		7,492,000		+1,798,000	
	Total positions		51		51		50		-1

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions....	51	50	-1
Full-time equivalent of all other positions.....	9	9	---
Average number of all employees.....	58	58	---
Personnel compensation:			
Permanent positions.....	$1,067,000	$1,093,000	+$26,000
Positions other than permanent.....	95,000	97,000	+2,000
Other personnel compensation.....	17,000	18,000	+1,000
Subtotal, personnel compensation.	1,179,000	1,208,000	+29,000
Personnel benefits.....	151,000	153,000	+2,000
Travel & transportation of persons...	49,000	54,000	+5,000
Transportation of things.....	6,000	6,000	---
Rent, communications & utilities.....	103,000	123,000	+20,000
Printing and reproduction.....	150,000	155,000	+5,000
Other services			
Payment to NIH Management Fund.....	256,000	286,000	+30,000
Other.....	880,000	1,197,000	+317,000
Supplies and materials.....	70,000	70,000	---
Equipment.....	40,000	40,000	---
Grants, subsidies, and contributions.	2,810,000	4,200,000	+1,390,000
Total obligations by object.....	5,694,000	7,492,000	+1,798,000

Authorizing Legislation

	1977 Authorization	1977 Appropriation Requested
Legislation		
Public Health Service Act		
Title III Part A - Research and Investigation in General (Section 301)	Indefinite	$6,992,000 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	4,587,000	4,187,000	5,303,000	5,392,000
1976	4,529,000	5,334,000	6,234,000	
1977	7,492,000			

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.

The figures presented in this table have been adjusted to reflect the transfer of functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years.

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	5,345,000	6,245,000	
1977	7,492,000			

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

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
	Amount Pos.	Amount Pos.	Amount Pos.	Amount Pos.
Gorgas Memorial Institute	$500,000	$860,000	$500,000	-$360,000
Scholars	1,950,000	1,950,000	3,700,000	+1,750,000
International Center	2,943,000	2,884,000	3,292,000	+408,000
Positions	51	51	50	-1
Total obligations	5,393,000	5,694,000	7,492,000	+1,798,000
Total positions	51	51	50	-1

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, and comparative studies of health 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 its central focus for international activities, the Special Foreign Currency Program, International Visitors and Visiting Program and the programming of health professionals of other nations.

The Fogarty International Center is requesting $7,492,000 in 1977.

Gorgas Memorial Institute

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
	Amount Pos.	Amount Pos.	Amount Pos.	Amount Pos.
Gorgas Memorial Institute...	$500,000	$860,000	$500,000	-$360,000
Positions.....	---	---	---	---

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 1976 and 1977

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. Of especial interest in this regard are the cause and effect relationships between these environmental factors and the major human health problems of atherosclerosis, hypertensive respiratory disease, cancer and certain nutritional derangements. In addition there are unique opportunities to pursue research in the delivery of preventive and therapeutic methods including large-scale clinical trials as well as the role of ancillary health personnel in health care delivery in community-oriented disease control programs.

Scholars

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
	Amount Pos.	Amount Pos.	Amount Pos.	Amount Pos.
Scholars.....	$1,950,000	$1,950,000	$3,700,000	+$1,750,000
Positions.....	---	---	---	---

Scholars

Fogarty Scholars-in-Residence

The Fogarty Scholars-in-Residence Program provides outstanding scientists and other scholars the opportunity to focus their attention on broad aspects of important issues in biomedical research. While in residence at the Center, the scholars singly and collectively engage in collaborative research with NIH and University scientists.

The unique environment at NIH offers an unusual opportunity for scholars to interact with large numbers of intramural staff scientists, initiate all types of meetings from formal international conferences to workshops and seminars. The involvement of these scholars provides an impetus to the progress of biomedical research and will, hopefully, hasten the solution to many of the disease problems confronting the world.

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.

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 1976 and 1977

The Fogarty International Center will continue to seek outstanding individuals for invitation and participation in the Scholars Program. The Senior International Health Program awarded 30 scholarships in its initial year of the Program. Announcements concerning this Program have resulted in the submission of a large number of applications from highly qualified scientists. 118 awards were made in fiscal 1976. Funds requested for fiscal 1977 will provide for 236 awards. 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.

International Center

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
	Amount Pos.	Amount Pos.	Amount Pos.	Amount Pos.
International Center...	$2,943,000	$2,884,000	$3,292,000	+$408,000
Positions.....	51	51	50	-1

International Center

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 1976 and 1977

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, a large number of conferences, seminars or workshops have been held and proceedings have been published and distributed.

Other elements of the advanced study program are individual studies which seek 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 abroad.

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 1977 budget provides for a net increase of $408,000. This includes increases of $119,000 for built-in items: $14,000 for within-grade pay increases; $6,000 for Federal Telecommunications System rate increases; $6,000 for service and supply rate increases; $17,000 for annualization of pay increases; $10,000 for postage rate increase; $5,000 for increase in per diem costs; $30,000 increase for Program Evaluation and General Expense and $30,000 increase for payments to the NIH management fund. A built-in decrease of $4,000 for one less day of pay is projected. In addition a program increase of $294,000 will support additional advanced studies and the publication of their results.

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)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$860,000	$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 1976: During fiscal year 1976 the Gorgas Memorial Laboratory continued research on malaria, leishmaniasis, trypanosomiasis, diarrheal disease and arboviruses of public health importance. Major contributions include the recognition of human disease due to vibrio parahemolyticus with profound implications for the seafood industry and the recognition of active loci of sylvan yellow fever. Studies of yellow fever were highlighted by successful control of mosquito vectors with experimental aerial spraying of malathion, this finding having enormous implications in the containment of this disease outside of the United Sstates.

Objectives in 1977: The Fogarty International Center has been active in affairs of the Gorgas Memorial Laboratory in the review of scientific programs and promoting interest in the Laboratory serving the scientific community of the United States. 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 Fogarty International Center. Implicit in this new 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. Of especial interest in this regard are the cause and effect relationships between these environmental factors and the major human health problems of atherosclerosis, hypertensive respiratory disease, cancer and certain nutritional derangements. In addition there are unique opportunities to pursue research in the delivery of preventive and therapeutic methods including large-scale clinical trials as well as the role of ancillary health personnel in health care delivery in community-oriented disease control programs.

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)

1976 Estimate		1977	Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
---	$1,950,000	Indefinite	---	$3,700,000

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 in 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. 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 disciplines.

The International 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 1976: In 1976, 118 awards were made to individuals 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 1977: In 1977, 236 awards will be made to applicants whose research proposals will have a direct effect upon research in 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: International Center (Public Health Service Act Title III Part A)

1976 Estimate		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
51	$2,884,000	Indefinite	50	$3,292,000

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 and 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 1976: This activity provides personnel support to all the center functions as well as the conference and study programs sponsored by the center which focus on current issues in biomedical and health research. During 1976, a number of conferences were held, involving several hundreds of foreign and domestic scientists. The results of these conferences are published and distributed to libraries, universities and institutions around the world.

Objectives in 1977: Continued activity in the advanced study area, 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.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

John E. Fogarty International Center for Advanced

Study in the Health Sciences

Transition Quarter Analysis

	1976 Estimate	Transition Quarter
Activity:		
Gorgas Memorial Institute	$860,000	$125,000
Scholars	1,950,000	271,000
International Center	2,884,000	739,000
Total	5,694,000	1,135,000

Explanation

The funds requested in the transition quarter will provide for a continuation of the programs of the Fogarty International Center at a level based on the President's Budget for FY1976.

TUESDAY, MARCH 2, 1976.

NATIONAL LIBRARY OF MEDICINE

WITNESSES

DR. MARTIN M. CUMMINGS, DIRECTOR, NATIONAL LIBRARY OF MEDICINE
DONALD S. FREDRICKSON, DIRECTOR, 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
LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
NORMAN D. MANSFIELD, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. NATCHER. Doctor, you have appeared before this committee in the past. Who do you have with you this time?

Dr. CUMMINGS. Kent Smith and Mel Day.

Mr. NATCHER. With your permission we would like to insert this statement in its entirety in the record and proceed with the questions.

Dr. CUMMINGS. That is all right.

BIOGRAPHICAL SKETCH

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.
1961–62, 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.
1942–44, U.S. Army, Pfc.

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.

Memberships: American Society for the History of Medicine. Board of Directors, Corgas 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 member, Alpha Omega Alpha. Honorary doctor of medicine, Karolinska Institute, Stockholm, Sweden, 1972. Honorary fellowship, College of Physicians, Philadelphia, 1973. Rockefeller Public Service Award, 1973. One hundred scientific and historical publications.

GENERAL STATEMENT

Mr. Chairman and members of the committee, in this Nation's Bicentennial year, the National Library of Medicine takes great pride in its many achievements accomplished over the past 140 years. Since its modest beginning in 1836, the National Library of Medicine has become an outstanding national resource which contains the most important collection of health sciences literature in the world. As part of the Surgeon General's Office of the Army, the Library originally consisted of a small collection of 30 books and journals. An Army surgeon, Dr. John Shaw Billings, developed and fostered the philosophy that the ever-increasing and important collection of biomedical publications was a resource that should be organized and utilized by health professionals in their efforts to promote the progress of medicine. That philosophy permeates the establishing legislation that authorized the creation of the National Library of Medicine in 1956.

Today the NLM's total collection of over 1.5 million items is organized in a most efficient manner consistent with facilitating timely dissemination of medical information to researchers, educators, and practitioners.

In the last 140 years, NLM has expanded well beyond its traditional role of curator of the published medical record to that of an active institution concerned with sustaining and operating a national biomedical communication network employing the latest communication technology and information science techniques.

Fiscal year 1977 at NLM will continue to be marked by new initiatives, innovation and significant challenges in the application of computer and telecommunications technologies to medical information transfer.

Substantial support for NLM's basic library services becomes a bigger challenge with each succeeding year. Demand for access to the literature is increasing at a rate of 25 percent in fiscal year 1976 and the cost of acquiring such materials will rise approximately 15 to 20 percent. Rising acquisition costs have forced more local hospital and clinical libraries to rely on NLM as a medical library backstop.

A second major challenge will be the difficult task of rapidly translating research results into clinical practice and public health, an assignment which we share with all of the Institutes and Divisions of NIH. Whereas the Institutes assume the responsibility for the accuracy of the content of the information we are preparing to provide the communications channels through which the messages reach the practitioners, patients, and other members of our society who have a need for this information.

The full resources and power of the national biomedical communications network will be brought to bear on the problem through the involvement of each NLM operating component.

BIBLIOGRAPHIC SERVICES

NLM continues to meet its traditional responsibilities of improving the flow of biomedical information by storing, retrieving, and disseminating the world's biomedical literature. To facilitate access to the literature, NLM produces bibliog-

raphies employing both manual search techniques and computer searches of online data bases; provides reference and loan services; prepares and publishes various materials for use by health science researchers and practitioners; and manages the Nation's online information retrieval network. NLM will provide approximately 400,000 reference and loan services during fiscal year 1976, an increase of 80,000 over fiscal year 1975. It is anticipated that the NLM will satisfy a requirement for 500,000 during fiscal year 1977.

Perhaps the prime tool of modern technology is the computer, and NLM has pioneered its use for bibliographic information storage and retrieval. A computerized reference retrieval system was installed in 1964 to help cope with increasing amounts of biomedical literature. This system, known as Medlars I, permitted both computerized production of Index Medicus and automated searches of the entire bibliographic data basee by health professionals. Last year a more sophisticated bibliographic processing system, Medlars II, was implemented successfully which has enabled NLM to develop new services and extend its existing services to a larger segment of the health community.

Medline (Medlars on-line) is now available in some 388 institutions at home and abroad. It facilitates rapid communication between the health professionals and the NLM's Medlars data base, which contains references to relevant medical literature. A total of 400,000 searches were performed last year through the NLM online system, and it is anticipated that approximately 500,000 searches will be performed in fiscal year 1976. The network will be expanded to provide access to many smaller hospitals and community-based academic institutions with preclinical and paramedical training programs. I am pleased to report that one of the newer capabilities has permitted the inclusion and searching of abstracts. It is anticipated by fiscal year 1977 over 100,000 author abstracts will be in the data base, thereby significantly augmenting the usefulness of Medline.

MEDICAL LIBRARY ASSISTANCE

The programs of medical library assistance form a vital component of the biomedical communications network. Through assistance to the network's regional medical libraries and grants to smaller medical libraries in hospitals and medical centers, NLM creates and fosters the institutional linkages which make the biomedical communications network a reality and the sharing of resources possible.

The regional medical libraries provide numerous services which have clearly demonstrated that cooperative library networking among health institutions is not only feasible but economically imperative. The foundation of the developing network has been the successful interlibrary loan program. Over 92 percent of the interlibrary loans made by the RML network are provided within 4 days. The number of loan services provided has been increasing at approximately 15 percent per year. By making its advanced online systems, such as Med'ine, available to the RML network, NLM greatly increases the availability of research results to all parts of the Nation.

To further enhance the capabilities of the RML network, the NLM awards resource project grants, which are intended to make current scientific literature readily available to the Nation's health professionals. 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 and studies ways of expediting the delivery of information through modern communications devices and automation techniques. In this manner resources are dedicated to upgrading the facilities and materials of local libraries within each region. Two other significant programs are: (1) Research grants which investigate and develop more effective information science and biomedical communications systems; and (2) training grants which provide assistance to health science information specialists in the application of computer technology to medical education and practice.

LISTER HILL NATIONAL CENTER FOR BIOMEDICAL COMMUNICATIONS

The Lister Hill National Center for Biomedical Communications is the primary research and development arm of the NLM. The Center provides technical information, support, and consultation to the health agencies and the health community on matters related to the broad application of computer and communication technology. It continues to develop and coordinate experimental communication networks and systems to improve health education, medical research, and

the delivery of health services. In the past we have reported to this committee the successes we have had with increasing the effectiveness of health care delivery and health education in remote areas of the Nation. We have developed and supported experimental interactive television networks in the New England area and have fostered demonstration projects which apply satellite communications technology in the Native villages of Alaska. New England's network is now completely supported through user fees, private contributions, and other sources of funding. This is a measure of its success.

The Alaska experiment demonstrated it was possible to extend the services of a hospital-based physician to distant villages by the use of telemedicine conferences. The closely linked Washington-Alaska-Montana-Idaho (WAMI) program demonstrated the benefits of regional sharing of resources in the medical education process. The communications network permitted faculty and students located on multiple campuses and at remote clinical training locations to partake of an integrated medical education program operated by the University of Washington in Seattle.

Based upon these early successes the LHC program has now begun a national experiment in broadband communication with the NASA launch in January of the joint Canadian-American communications technology satellite (CTS). There is a great need to share manpower in health education, in accessing medical consultative services, and in disseminating the results of biomedical research. The health experiments which are planned for the CTS satellite afford the health agencies an opportunity to develop models and design systems for sophisticated teleconferencing, for developing regional education programs, and for improving the transfer of biomedical information. These experiments and demonstrations will permit us to identify those communication and information transfer modes which are best suited for a national health broadband communications network.

An additional Center activity which holds great promise is the development within the National Library of Medicine of a modest Learning Resource Laboratory designed to consolidate computer-based educational resources in a single area. It is desirable to have the power of the computer available to libraries, computer-based education, and medical practice at those locations where providing access to large computers is presently either not feasible or very costly. Within this modest laboratory, we plan to develop and test relatively inexpensive combinations of various minicomputers and terminals which are easy to access and can manipulate data to satisfy individual application needs at costs which the user can afford.

As one looks to fiscal year 1977, efforts will be targeted at developing new and improved uses of technology for scientist to practitioner communications. The Center's expertise in telecommunications and satellite communications offers a unique opportunity for televised clinical conferences and for demonstration and staff services between NIH and other centers within the biomedical community. These same networks will improve continuing medical education, public education, and remote patient presentation for diagnosis and recommended treatment.

TOXICOLOGY INFORMATION PROGRAM

The toxicology information program (TIP) collaborates extensively with other Federal agencies, such as the Food and Drug Administration and the Environmental Protection Agency, to develop, organize, and operate a computer-based toxicology data bank. Through its information services, TIP makes results of toxicological investigations readily available to those engaged in conducting research, and monitoring the environment.

During the past year, TIP continued to expand its highly successful online bibliographic retrieval service Toxline. The data base was expanded to include special literature files which serve to improve coverage in specific areas of mutagenesis, teratology, and heavy metal toxicology. Toxline contains literature published during the most recent 5 years and is available online through the NLM computer. The data base currently contains 420,000 citations and is expected to reach 590,000 by the end of fiscal year 1977. In fiscal year 1976 approximately 25,000 online searches will be performed, an increase of 25 percent over fiscal year 1975. In planning for fiscal year 1977 we have projected a 20-percent growth factor in online searches and a 10-percent increase in the number of pages of offline prints.

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TIP will develop plans for an information system which will attempt to identify the potential hazards of products about to enter the marketplace. Such a system when developed should assist in efforts to protect the public from environmental hazards prior to public marketing of commercial products.

AUDIOVISUAL SERVICES

The National Medical Audiovisual Center (NMAC) continues to serve health professionals by acquiring, developing and distributing audiovisual instructional materials which are utilized in the teaching and practice of medicine, dentistry, and the allied health professions. Materials developed by NMAC with the cooperation of professional societies and academic health centers are currently used throughout the Nation's biomedical community. The audiovisual teaching packages developed by NMAC for sale increased threefold from 36 packages in fiscal year 1975 to a total of 108 in fiscal year 1976.

For the last 5 years, NMAC and the Bureau of Health Manpower, Health Resources Administration, have cosponsored a collaborative program called the learning resources program to improve the use and effectiveness of learning materials in health science schools. This program has recently been enhanced by the development of an educational research activity which will complement the audiovisual development, evaluation, training, and advisory service functions which have been carried out over the past several years. These activities study and promote learning programs which make full use of modern instructional media and systems.

NMAC has also established a regional center to design, develop and test teaching strategies through cooperative efforts with regional educational institutions.

In addition, NMAC has implemented its Avline (audiovisuals online) system which facilitates access by health professionals to the most effective instructional material for classroom and self-instructional use. Recently initiated with the entry of more than 700 references to effective instructional materials, the data base should eventually contain over 10,000 items. By the close of fiscal year 1976 approximately 2,000 references will have been entered.

SUMMARY

As the National Library of Medicine prepares to meet the challenges of the future it is keenly aware of the ever-growing biomedical information requirements of the health community. We remain committed to disseminating medical information to the Nation's health professionals in the most efficient and timely manner. NLM programs have and will continue to be characterized by innovation and technological advancements. Significant progress in biomedical communications technology and networking will be markedly enhanced with the construction of the new Lister Hill Building. We are pleased to report to the committee that the architectual and engineering drawings are ready to be issued for construction bids.

In summary, Mr. Chairman, our request for fiscal year 1977 is $35,234,000, an increase of $5,990,000 over the amount available for obligation in fiscal year 1976. The net increase reflects $1,575,000 for mandatory requirements and $4,415,000 for the expansion of NLM programs. I shall be pleased to answer any questions and supply additional information desired for the record.

BUDGET INCREASES

Mr. NATCHER. You propose an increase of 70 percent in your request. Can you explain why these increases are necessary this year?

Dr. CUMMINGS. First, I should like to point out, if you examine the budget of the National Library of Medicine over a 5-year period, this is the first time I have been privileged to come before this committee with a significant increase in our budget. I think in part we owe this support to the Director of NIH.

Specifically the increases proposed are to cover the following activities. The Lister Hill National Center for Biomedical Communications is now poised to make significant contributions to the transfer of medi-

cal information to the community at large using new communications technology. With respect to het extramural program which you mentioned, this is the first time in recent years that the Naional Library will have an opportunity to fund more than 15 percent of the approved grants which have come before it. There have been many very fine proposals which, in our judgment, will support the national base for improved library services which have gone unfunded in the past. We hope to partially rectify that situation.

We have also within this increase a program for our National Medical Audiovisual Center providing for evaluation and distribution of educational materials used by the health professions generally.

The most important increase in my judgment is for the basic support of library operations within our institution where for many years we have been struggling with a rather large annual increase in demands for service. These demands average 20 to 25 percent per year and we believe we need to reinforce this direct service operation from this budget. One special program I should identify also which would benefit from the overall increase is the toxicology information program which is planning in the near future to develop a computer based information system which we hope will assist in an early warning system to identify potential hazards in products before they are marketed. These are the activities which will share in the increases which you have identified.

RESEARCH DISSEMINATION

Mr. NATCHER. With respect to your request for increase in grant and contract funds for the Lister Hill Center, can you be more specific as to the type of activities you plan to support with the $2 million for research dissemination?

Dr. CUMMINGS. Yes, sir. The principal one is to put in place, the ground terminals which will be necessary to capitalize upon the new communications technology satellite which has been launched by our Government and the Canadian Government. This satellite known as CTS will be used principally for the linkage and dissemination of health information to a large segment of our country which are either somewhat deprived or unusually rich in sources of medical information. Specifically, we are planning to provide stations in Alaska, Washington, Montana, Kentucky, and Colorado, with a base in Bethesda, which will permit the NIH staff to translate and disseminate new information useful to health practitioners.

This is the largest program of this type we have even undertaken and it will require most of the fund requested.

MEDICAL LIBRARY ASSISTANCE

Mr. NATCHER. You are also requesting a large increase for medical library assistance. Again, what kind of grants and contracts are you planning for?

Dr. CUMMINGS. With the exception of support of the regional medical libraries, all the support through the Medical Library Assistance Act is provided through the grants mechanism.

In extramural program funds will be used for resource grants to smaller community and large medical institutions throughout the coun-

try to improve their library services. It will also assist in the training of health professionals in the utilization of computer technology and will provide support for special information technology. Also it will provide the basic support for the 10 regional medical libraries which are part of our national medical library network. These are the principal areas of program utilization of these funds.

INTEGRATION OF SYSTEMS

Mr. NATCHER. Over the last several years you have established a rather elaborate array of different systems for serving the scientific community. How integrated are these systems both at the input and service end of the line?

Dr. CUMMINGS. Mr. Chairman, the computer-based systems operated by your national library of medicine are coordinated centrally. We prepare the data bases and the information put into the system and operate the central computer facility. The computer-based systems use standardized programs so that we can share the various data base information through a common set of programs. Also we use a common communications network so that a user searching for information goes to one point of entry and can search the various data bases available to him. In the satellite communications our role is somewhat different. We don't operate the satellite in space, of course, but we do coordinate the network use through which the health programs will be transmitted. We work with the other health agencies, particularly those in the health service areas who determine the content of the information to be transmitted through the system.

USER CHARGES

Mr. NATCHER. I know you charge a small fee for certain of your services. Does this fee represent a significant source of income and is there a possibility of putting the system on more of a fee-for-service basis?

Dr. CUMMINGS. It is correct that we have a user charge for our specialized computer services. The user is expected to pay for the communication costs to access the system. In fact, this provides recovery of all the communication costs and this year will provide approximately $100,000 to be returned to the Treasury. We don't believe at this juncture at least, that it is appropriate for us to increase these charges. I believe I have reported to this committee previously that we have doubled our charge for computer services during the past year from $8 an hour to $15 an hour for prime time. We feel this is an appropriate charge sufficient to inhibit any frivolous or trivial requests for services but not too high preventing a user in need of this service to obtain it.

Mr. NATCHER. How much in user fees do you expect to collect in 1976; and how much in 1977?

Dr. CUMMINGS. I will ask Mr. Smith to answer that.

Mr. SMITH. Around $800,000 in 1976 and a little over $1 million in 1977.

Mr. NATCHER. Thank you.

Following up on this, can you tell me what average user charge would be for a Medline request if there was 100 percent passthrough based on cost?

Can you give me some idea on this?

Dr. CUMMINGS. I can give you an idea now and provide further information for the record. The average Medline charge is approximately $2. In the old batch mode system a comparable cost was $60 to $75 a search. The power of new technology is reflected by this tremendous drop in cost. This represents about half of the total cost of the search since we pay to acquire the literature analyzed and process it for the computer store. So roughly I would say we have about a 50–50 subsidy in terms of cost.

The total cost associated with providing the estimated 400,000 Medline searches in fiscal year 1976 is $1,472,000. If the library operated on a 100-percent passthrough basis, the unit cost would be $3.68 per search. Of the total costs, user charges offset approximately $712,000 or $1.78 per search. The library appropriation provides funds for the in-house processing requirements associated with operating Medline services. This will equate to approximately $760,000 in fiscal year 1976 or $1.90 per search.

I should add that the national library would have to index and catalog literature to provide the users with our publications, the various indexes and biblographies. So, we are really charging the customer only for entry into the computer system.

EXPANSION OF MEDLINE

Mr. NATCHER. I have heard some discussion in past years as to the possibility of expanding the Medline bibliography to include more information on problems of delivery of service as opposed to strictly clinical problems. Do you feel the present indexing is sufficient to cover these issues?

Dr. CUMMINGS. Mr. Natcher, we believe within the present data base, there is a comprehensive coverage of the scope of medicine including basic science, clinical medicine, public health and health care delivery. That is not to say that everything which is published in these various fields is included in the data bases. Some selection is made by a critical review board to identify those materials thought to be of original, substantive content and not repetitive.

It is my view that in almost any area of medicine, with the rapid growth of medicine, that we could enlarge the data base to achieve more coverage. However, there is no evidence that such an increase in coverage would better serve the needs of health care delivery as your query suggests. Overall, I think our users are quite pleased with the services we are providing. The tradeoff is whether we want to make this an enormous data base which would be costly and difficult to manage or one sufficiently comprehensive so as to respond to a large percent of queries.

REGIONAL MEDICAL LIBRARY PROGRAM

Mr. NATCHER. As to the regional medical library, your expansion into more isolated areas, is this more of the same or are there special problems in serving these institutions, Doctor?

Dr. CUMMINGS. I would say the new dimension of the regional medical library program can be characterized as outreach. We are persuading each of the regional libraries that their responsibility is to provide equal access to qualified users no matter where they may reside. I think we have good evidence that a determined effort is being made to see that the isolated user has the same entry into the system as someone who resides close to the center.

CONTINUING MEDICAL EDUCATION COORDINATION

Mr. NATCHER. I am interested in your role in the field of continuing medical education. Can you tell me specifically how your efforts are coordinated with other HEW organizations and with the professional organizations and institutions?

Dr. CUMMINGS. We don't have a primary role in the generation of materials for continuing health professional education, but we do maintain a strong supportive role for all professional organizations and associations and educational institutions which need special information for their own operations. In this context, we work very closely with the Health Resources Administration through our National Medical Audiovisual Center where teaching materials are acquired, evaluated and loaned to professional groups or individuals for their use. The Lister Hill Center has an extensive program with institutions which use computer-assisted instruction as a new modality for continuing education. I can summarize my answer by saying we are involved in the provision of educational materials but don't assume the responsibility for selecting those materials which should be studied.

NATIONAL MEDICAL AUDIOVISUAL CENTER

Mr. NATCHER. All right, Doctor. With respect to your audiovisual indexing and information system, is this restricted to materials for professional information or are you coordinating this activity with the general health activities of the department?

Dr. CUMMINGS. Our National Medical Audiovisual Center is primarily concerned with materials judged to be useful to the health professional community and only secondarily are we concerned with the provision of materials to the public at large, or health education more generally. We do coordinate our activities with other organizations in the same field, but I think it is fair to say that I know of no other institution which has the same capacity and the same facility through which to serve the audiovisual needs of the health professionals.

FOREIGN USERS

Mr. NATCHER. Your justification refers to the foreign medlar centers. What role do these centers play and how well established are they?

Dr. CUMMINGS. We have a number of bilateral agreements with institutions at home and abroad. In sophisticated countries we allow selected institutions access to our data bases in return for which they

provide the indexing and cataloging of an enormous amount of literature which is generated abroad.

In fact, there is a quid pro quo relationship though which the national library gains input into its system and eight countries which are partners in this arrangement, gain access to our data bases.

TOXICOLOGY INFORMATION PROGRAM

Mr. NATCHER. Now, Doctor, turning to your toxicology activities, could you explain to me how the new early warning system works and specifically what costs are associated with it?

Dr. CUMMINGS. First I should say there is no such early warning system in being. We have suggested that we might develop such a system, and that this be based on the knowledge available to chemists, pharmacologists, and toxicologists who can examine chemical structures and families of related structures and predict that certain toxicity or adverse reaction might occur in a number of related compounds.

Because the toxicology data bank is building to a point where we now have a sufficient number of materials as pesticides, for example, we believe that we can organize these data in a manner in which a sophisticated, knowledgeable, pharmacologist or toxicologist could query the system and get data which might provide a clue that a new product might be expected to have some adverse effect on man or his environment.

I do want to point out that this is a plan. It is not a reality. The budget before you request funds with which we could go ahead if they were made available.

Mr. NATCHER. Can you tell the committee who the users of the laboratory and animal data bank are and how many requests for this information are you currently receiving?

Dr. CUMMINGS. The present parties interested in the development of this data bank are principally Government agencies such as FDA, EPA, the National Cancer Institute, and a large number of our drug and pharmaceutical companies, which are generously providing data for input into the system.

The system is still in the building phase and the data are being stored in the data bank. We anticipate that the same organizations which are putting their information into the system will, in fact, be the principal users of the system.

The National Academy of Sciences through a specialized advisory group has assumed the responsibility for the advisory and evaluative role of the performance of this system, and I think perhaps at this time next year, Mr. Natcher, I would be in a better position to tell you about user reaction and user response, which we believe is the most important element in evaluation.

Mr. NATCHER. Mr. Michel?

LIBRARY REFERENCE AND LOAN SERVICES

Mr. MICHEL. How do you account for the 25-percent increase per year in requests for your reference and loan services?

Dr. CUMMINGS. The establishment of a network of medical centers providing on-line reference services to the world's most important medical literature has resulted in increased demands for copies of arti-

cles cited. This growth in demands parallels the growth of on-line bibliographic services.

Mr. MICHEL. Is this rate increase likely to continue for the foreseeable future?

Dr. CUMMINGS. The rate of growth in demand for interlibrary loans will probably reduce somewhat since the on-line services are now increasing at a lesser rate. We are projecting that further growth over the next 5 years will level off to an annual rate of about 10 percent or less.

LIBRARY ACQUISITION COSTS

Mr. MICHEL. Are acquisition costs likely to continue to rise at a 15- to 20-percent rate, or do you expect a stabilization?

Dr. CUMMINGS. At the present time the largest percent of increase is in the area of journal subscriptions. Publishers' costs continue to rise at approximately 15 percent per year. This is the result of increased paper and production costs, and increased cost of mailing which has recently added another 3- to 5-percent increase in subscription costs. We believe that a 10- to 15-percent rate of increase for acquisitions will probably continue.

TOXICOLOGY PROGRAM

Mr. MICHEL. You indicate that the toxicology information program is developing plans for an information system which will attempt to identify the potential hazards of products about to enter the marketplace. Who is going to provide the input in such a system?

Dr. CUMMINGS. The toxicology information program will not be evaluating or commenting on products either by their commercial or brand names. The evaluation activity will not be consumer oriented. Reports will be made by chemical substances and not by product formulations. Reports will be based on contents of scientific studies being published in scientific journals. Chemical substances will be discussed by scientific names. Reports will not deal with new products as a class but only with general chemicals which might be in old products, considered for new products, or as yet not used in products. Input for this activity will come from scientific journals, monographs, papers presented at national scientific meetings and studies carried out by Government agencies.

Mr. MICHEL. What guidelines will you be establishing to protect against the abuse of such a system? We certainly want to make certain that products are not unfairly brandished as a hazard to one's health, do we not?

Dr. CUMMINGS. The system will be protected against abuse because the reports will be disseminated primarily to Federal agencies through the DHEW Committee To Coordinate Toxicology and related programs. This committee is staffed by scientists representing the health agencies of the Department and—as observers—health agencies from other Government departments. The committee would evaluate reports furnished by the toxicology information program before dissemination to the agencies represented.

DISTRIBUTION OF INCREASES IN PROGRAM BUDGETS

Mr. MICHEL. Which programs are budgeted to receive most of the increase you are requesting in 1977 over this year?

Dr. CUMMINGS. The $5.9 million increase which the library is requesting will be used in three areas. Approximately $1.6 million of the increase will support medical library development of resources and systems necessary to bring the latest health science information to researchers and clinicians throughout the Nation. This will be accomplished in part by strengthening the regional medical library network and by extending library services to smaller and more remote institutions. An additional $2 million will be used by the Lister Hill National Center for Biomedical Communications in its efforts to improve the effectiveness and efficiency of biomedical communications and improve the dissemination of NIH research results.

Primary efforts will be targeted at developing new and improved uses of technology for scientists to practitioner communications. The remaining $2.5 million will be used to support NLM's basic library services which have suffered the most during the previous years of level budgets.

DISSEMINATION OF RESEARCH RESULTS

Mr. MICHEL. Have you had maximum cooperation from other institutions in your dissemination efforts?

Dr. CUMMINGS. Contact with all Institutes has taken place. In addition, at the direction of the Director, NIH, a task force for implementation has been established. The Director of the Lister Hill Center is a member of this task force. These efforts are, therefore, being pursued aggressively on a NIH-wide basis.

Mr. MICHEL. Are some of the Institutes a little slower than others in their efforts to disseminate their research findings? If so, which ones?

Dr. CUMMINGS. The problems of disseminating research results are not uniform for all the Institutes, nor are the organizations and resources available for this purpose. The manifest progress varies from Institute to Institute also as a function of level of interest or concern. As a result of these considerations, the Director of NIH is vigorously pursuing the implementation of a total NIH effort to improve dissemination of research results.

NEW LISTER HILL BUILDING

Mr. MICHEL. Will you have any extra space in the new Lister Hill Building or will it all be utilized at the outset?

Dr. CUMMINGS. At the time of occupancy in the fall of 1975 we expect to be at 75 percent of capacity. This is based on the assumption that employment at the National Library of Medicine will increase by 80 positions during the next 3 years. These additional positions will be required in order to optimally utilize the new specialized functions and facilities that will be in the new building. Special purpose space and facilities will be used by other health-related agencies for communications conferences, experiments and demonstrations.

RESEARCH AND DEVELOPMENT PROJECT CONTRACTS

Mr. MICHEL. I note in your justification a sizable increase, from $4 million to $6.7 million, for "Project Contracts" under "Other Services." What is that for, and why the substantial increase?

Dr. CUMMINGS. The Library has placed increased emphasis on pursuing research and development within the Lister Hill Center. Two laboratories, one related to the general areas of computer technology, and the other to the general area of broadband communications technology are being developed. The first is the Learning Resources Laboratory which will be used by the Computer Technology staff to investigate the potential for using small and less expensive computers, minicomputers, to make available substantial computer power to a large number of widely dispursed users at affordable costs. The second laboratory is an experimental broadcast studio which will enable the Center's Communication Engineering staff to explore advanced technology as a medium for extending effective educational programs to the health community; for improving health care delivery; and for enabling more effective dissemination of research results.

PROCEDURES FOR COMPUTER REQUESTS

Mr. ROYBAL. How would an individual practitioner go about requesting information you have in your computer files? In what form is the information sent to him? What is the cost of requesting such information?

Dr. CUMMINGS. Physicians interested in searching the Medline system reach our files through their nearest Medline Center. The search will usually be performed by a trained analyst and the practitioner will receive a computer printout listing the citations to journal articles which match his information need. The exact procedure varies from one Center to another; some receive requests in written form, others by telephone, and in some cases the requester is present for the reference interview and the actual search. Costs vary as well, ranging from free service to a maximum charge of $8.50.

MEDLINE ACCESS

Mr. ROYBAL. How do you choose the institutions that are linked into your computer system? What countries outside the United States are linked into the system? Do they contribute money to finance the system?

Dr. CUMMINGS. Institutions with a substantive need for health-related information and appropriate resources to provide on-line service may apply to become a Medline Center. Foreign Medline Centers exist in Canada, Germany, Sweden, Australia, France, England, and Japan. The World Health Organization also operates a Medline Center. The Library has quid pro quo arrangements with these countries which provide indexing of foreign literature in return for access to the Library's Medlars data base.

COMMUNICATION TECHNOLOGY SATELLITE

Mr. ROYBAL. What is the projected amount you will spend on Joint Canadian-American Communication Technology Satellite?

Dr. CUMMINGS. It is currently estimated that during the period of fiscal year 1975 through fiscal year 1978 the Lister Hill Center will spend approximately $1,874,000 on the CTS program.

AUDIOVISUAL PACKAGES

Mr. ROYBAL. You indicated you developed 108 audiovisual packages for sale. How many were sold? What were the gross receipts from these sales?

Dr. CUMMINGS. Approximately 8,018 packages have been sold since July 1973. The sales program is conducted by the National Audiovisual Center, General Services Administration. They make this material available at no profit to the biomedical community. It is estimated that the gross receipt from these sales has been approximately $260,000 since July 1973.

MEDLINE

Mr. CONTE. How much use does Medline get per year?

Dr. CUMMINGS. Last fiscal year, more than 400,000 searches were performed throughout the Library's on-line network. This fiscal year, we expect searches to pass the half million mark.

Congressman CONTE. What are the current user charges for Medline? How does this compare to user charge of commercial computer time?

Dr. CUMMINGS. The current charges for Medline are $15 per hour during prime time, which is defined as 10 a.m. to 5 p.m. eastern time, and $8 per hour at other times. In addition, there is a 10 cent per page charge for off-line printing and mailing of search results. The commercial charge for similar retrieval services costs from a low of $35 per hour, for access to the Educational Resources Information Center which is operated by the Systems Development Corp., to approximately $100 per hour. Service from a data base of the size of Medline varies from $70 to $100 per hour from a commercial vendor depending upon costs, profit objective, and usage level.

LISTER HILL CENTER BUILDINGS

Mr. CONTE. What progress has been made in construction at Lister Hill since last year?

Dr. CUMMINGS. The Lister Hill Center Building will soon become a reality now that the Congress has appropriated $26 million for its construction. The architectural and engineering drawings were completed last July and the General Services Administration is prepared to advertise for construction bids as soon as the funds are apportioned and necessary impact statements have been processed. Construction could commence in the fall of 1976. The initiation of this project will

not only alleviate the severe space problem within the present library but will provide specialized facilities in order to enhance communications systems for health education, research and practice in this nation.

THE LIBRARY'S ROLE AS A NATIONAL INFORMATION RESOURCE

Mr. CONTE. I have seen that partially because of the rapidly increasing demand for medical literature and because the costs of acquisition have risen 15 to 20 percent, your facility is increasingly being relied on to be a national information resource. Is this a good development or should the responsibility be spread out more geographically and institutionally?

Dr. CUMMINGS. The total service load for health information services is substantially higher than that presently provided by the Library. Of about 750,000 interlibrary loans provided to the health care community, two-thirds are provided through the Regional Medical Library Network. Decentralization of services has been a significant factor in Regional Medical Library development. This effort has not only improved service at the local level, but has created more ready access to our services, which in turn has generated increasing workloads. The Library will continue to share the workload with the major medical libraries in the Regional Medical Library Network and to augment the resources in the regional and local libraries to share these increasing workloads.

NATIONAL MEDICAL AUDIOVISUAL CENTER USAGE

Mr. CONTE. How much use does the audiovisual facility in Atlanta get?

Dr. CUMMINGS. A major workload of the National Medical Audiovisual Center relates to its distribution activities which provide the biomedical user community with access to relevant instructional materials. During fiscal year 1976 an estimate 60,000 audiovisual loans will be provided. Demand for these loans will increase about 10 percent during fiscal year 1977. The Center also provides advisery services which are designed to encourage direct interchange and assistance to the health professional community. This is accomplished through site surveys, in-house consultations, and training programs in planning, design and application of audiovisual instructional technology to problems of on-campus learning environments, systems and equipment. During fiscal year 1976 over 500 individuals will participate in such workshops and 75 educational facilities and systems consultations will be undertaken.

SATELLITE COMMUNICATIONS SYSTEM

Mr. CONTE. Can you tell us what has happened since I talked to you last year with the Satellite Communication System?

Dr. CUMMINGS. The Lister Hill Center has been engaged in a series of experiments and demonstration projects which apply satellite communications technology to the solution of recognized problems in health education and the delivery of health services. Two satellites in the Applications Technology Satellite (ATS) series have been involved, namely ATS–1 and ATS–6. The Lister Hill Center's active

participation in the Satellite Communication System terminated with the expiration of all applicable contracts during the last calendar year. However, the State of Alaska has assumed responsibility for ATS–1 programing and with aid from the Indian Health Service has utilized the satellite to support the Alaskan native population.

Mr. CONTE. Do you plan to expand upon the Washington/Alaska/Montana/Idaho program, which seems to have worked out well?

Dr. CUMMINGS. Yes; we will continue to support the WAMI program through participation in a series of experiments which will extend the ATS experience through the Joint Canadian-American Communications Technology Satellite (CTS).

TOXLINE

Mr. CONTE. Who now has access to Toxline?

Dr. CUMMINGS. Toxline, the National Library of Medicine's Toxicology Information Retrieval Service On-line, is available domestically to any professional organization that signs an agreement with NLM for the service, and has been trained in toxline operation. There are 220 organizations subscribing to Toxline; of these, 111 are commercial organizations, 77 are academic institutions, and 28 are Government facilities. Approximately five new organizations subscribe to Toxline each month.

LEARNING RESOURCES PROGRAM

Mr. CONTE. Do you have any hard results from the collaborative learning resources program?

Dr. CUMMINGS. This program has provided a multidisciplinary emphasis on the improvement of health sciences instruction that has led to the development of 260 new instructional media, training of over 2,500 faculty members in how to use instructional technology in schools, the screening of 11,200 instructional media to determine those most effective for faculty reference through computerized information systems. A large number of educational institutions participate in these efforts. These activities have increased the impact of educational technology within health professional schools. Without this collaboration, the cooperation and interest of organizations such as the Association of American Medical Colleges, Association of American Dental Schools, Association of Pediatric Department Chairmen, and the American Physiology Society in the development and sharing of more effective instructional materials could not have been gained.

Mr. NATCHER. Dr. Cummings, we want to thank you and your associates for appearing before our committee at this time in behalf of your budget request for fiscal year 1977. It is always a pleasure to have you.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

FY 1977 Budget

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Amounts Available for Obligation 1/

	1976 Estimate	1977
Appropriation	$29,065,000	$35,234,000
Comparative transfer from:		
"Office of the Director" for standard level user charge	179,000	---
Total Obligations	$29,244,000	$35,234,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $2,000,000; 1977 - $2,000,000.

Summary of Changes

1976 Estimated Obligations	$29,244,000
1977 Estimated Obligations	35,234,000
Net Change	5,990,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-In:				
1. Annualization of 1976 Pay Cost Increases	---	519,000	---	+ 165,000
2. Within-Grade Pay Increases	---	200,000	---	+ 235,000
3. FTS Rate Increases	---	160,000	---	+ 21,000
4. Literature Acquisition	---	775,000	---	+ 100,000
5. Increase Cost of Service and Supply	---	120,000	---	+ 22,000
6. Computer Rental Increase	---	1,842,000	---	+ 138,000
7. Postage Cost Increase	---	318,000	---	+ 99,000
8. Non-Competing Continuation Costs	---	5,203,000	---	+ 417,000
9. Payment to NIH Management Fund	---	1,620,000	---	+ 356,000
10. Standard Level User Charge	---	179,000	---	56,000
Subtotal, Built-In Increases	---	---	---	+1,609,000
B. Program:				
1. MLAA - to provide support for scholarly research and continuing medical education	---	6,433,000	---	+1,150,000
2. Lister Hill Nat'l Center for Biomedical Communications - for the application of advanced computer and communication technology to the solution of biomedical communication and information dissemination problems	24	2,760,000	-1	+1,945,000
3. Nat'l Medical Audiovisual Center - for the development of instructional media in a variety of health science disciplines	100	2,981,000	---	+ 495,000
4. Library Operations - for the continuation of basic library services and the modest expansion of services to the biomedical community	252	10,014,000	-2	+ 551,000
5. Toxicology Information - for the modest expansion of the Toxicology data base to include an "early warning" system on potential hazards of chemicals about to enter the market place.	17	1,866,000	-1	+ 275,000
Subtotal, Program Increases	---	---	-4	+4,416,000
Total Increases	---	---	-4	+6,025,000

Summary of Changes (cont'd)

1976 Estimated Obligations	$29,244,000
1977 Estimated Obligations	35,234,000
Net Change	5,990,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Decreases:				
A. Built-In:				
1. Employment savings - effect of one day less pay in FY 1977	472	11,088,000	---	- 35,000
Total Decreases	---	---	---	- 35,000
Total Net Change	---	---	-4	5,990,000

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Obligations by Activity

Page Ref.		1976 Revised President's Budget Pos.	1976 Revised President's Budget Amount	1976 Appropriation Pos.	1976 Appropriation Amount	1977 Estimate Pos.	1977 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
	Medical Library Assistance								
241	Total	---	6,333,000	---	6,433,000	---	8,000,000	---	+1,567,000
	Direct Operations:								
244	Lister Hill Nat'l Center for Biomedical Communications	23	2,740,000	24	2,760,000	23	4,730,000	-1	1,970,000
247	Nat'l Medical Audiovisual Center	100	3,096,000	100	2,981,000	100	3,551,000	---	+ 570,000
249	Library Operations	250	10,169,000	252	10,014,000	250	10,933,000	-2	+ 979,000
251	Toxicology Information	16	1,873,000	17	1,866,000	16	2,166,000	-1	+ 300,000
253	Program Management	79	5,066,000	79	5,011,000	79	5,559,000	---	+ 548,000
	Standard Level User Charge	---	179,000	---	179,000	---	235,000	---	+ 56,000
	Subtotal	468	23,123,000	472	22,811,000	468	27,234,000	-4	+4,423,000
	Total Obligations	468	29,456,000	472	29,244,000	468	35,234,000	-4	+5,990,000

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions.....	472	468	-4
Full-time equivalent of all other positions.....	40	40	---
Average number of all employees.....	531	527	-4
Personnel compensation:			
Permanent positions.....	8,877,000	9,607,000	730,000
Positions other than permanent.....	424,000	474,000	+50,000
Other personnel compensation.....	116,000	116,000	---
Subtotal, personnel compensation..	9,417,000	10,197,000	+780,000
Personnel benefits.....	936,000	1,021,000	+85,000
Travel and transportation of persons.....	170,000	175,000	+5,000
Transportation of things.....	30,000	34,000	4,000
Rent, communications and utilities.....	2,372,000	2,609,000	+237,000
Printing and reproduction.....	479,000	496,000	+17,000
Other services:			
Project contracts.....	4,000,000	6,740,000	+2,740,000
Payment to NIH Management Fund.....	1,799,000	2,211,000	+412,000
Other.....	2,189,000	2,232,000	+43,000
Supplies and Materials.....	314,000	314,000	---
Equipment.....	330,000	330,000	---
Literature.....	775,000	875,000	+100,000
Grants, subsidies and contributions.....	6,433,000	8,000,000	+1,567,000
Total obligations by object.....	29,244,000	35,234,000	+5,990,000

Authorizing Legislation

Legislation	1977 Authorized	1977 Appropriation Requested
Public Health Service Act		
Section 381 - Purpose and Establishment of Library	Indefinite	$27,234,000 2/
Health Services Research, Health Statistics, and Medical Libraries Act of 1975		
Section 393 through 397	$20,000,000	8,000,000 2/
Total		$35,234,000

2/ Funding estimate only

National Library of Medicine

Comparable

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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 1/
1974	24,994,000	25,796,000	25,796,000	25,426,000 2/
1975	27,738,000	28,048,000	29,348,000	28,848,000
1976	28,815,000	28,994,000	29,744,000	
1977	35,234,000			

1/ 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.

2/ Appropriation after reduction as authorized by P.L. 93-192.

National Library of Medicine

Actual

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	28,850,000
1976	28,815,000	28,815,000	29,565,000	
1977	35,234,000			

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 as authorized by P.L. 93-192.

3/ Excludes Medical Library Assistance Grants not considered by House due to lack of legislative authorization.

Justification

National Library of Medicine

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Medical Library Assistance	6,333,000	6,433,000	8,000,000	+1,567,000
Positions	---	---	---	---
Direct Operations:				
Lister Hill National Center for Biomedical Communications.	2,740,000	2,760,000	4,730,000	+1,970,000
Positions	23	24	23	- 1
National Medical Audiovisual Ctr.	3,096,000	2,981,000	3,551,000	+ 570,000
Positions	100	100	100	---
Library Operations	10,169,000	10,014,000	10,993,000	+ 979,000
Positions	250	252	250	- 2
Toxicology Information	1,873,000	1,866,000	2,166,000	+ 300,000
Positions	16	17	16	- 1
Program Management	5,245,000	5,190,000	5,794,000	+ 604,000
Positions	79	79	79	---
Subtotal	23,123,000	22,811,000	27,234,000	+4,423,000
Positions	468	472	468	- 4
Total Obligations	29,456,000	29,244,000	35,234,000	+5,990,000
Positions	468	472	468	- 4

General Statement

The National Library of Medicine is the world's largest research library devoted to a single scientific or professional discipline and the prime resource in the United States for biomedical information. In addition to acquiring, organizing, and disseminating such information through the use of computerized systems, interlibrary loans, and more conventional library services, NLM has developed a National Biomedical Communications Network to link major health care facilities, medical education centers and research institutions. Through assistance to the network's Regional Medical Libraries, as well as grants to smaller medical libraries in hospitals and centers, NLM applies computer and communications technology to the improvement of nationwide health information transfer.

The primary research and development arm of the NLM is the Lister Hill National Center for Biomedical Communications. The Center provides technical

information, support and consultation to the health agencies and health care professionals on matters related to the broad application of computer and communications technology.

An additional role which has evolved in recent years is the conduct of research and development predicated on anticipated future needs of the health agencies and the health community. In the performance of these functions the Lister Hill National Center for Biomedical Communications has provided the resources necessary to support the planning and development of experiments and prototype models in applying computers and communications to facilitating health education, health care delivery and health research. The Center will continue to concentrate its efforts on developing communications support for health professional education where a small investment can have the largest impact on the quality of health care. Specifically, these activities fall within five programmatic areas: broadband biomedical communications; computer-based education; computer technology research and development; postgraduate education for the practicing health professional; and coordination of biomedical communications for DHEW.

NLM continues its traditional responsibilities of improving the flow of biomedical information by storing, retrieving and disseminating the world's biomedical literature. To facilitate access to the literature, NLM produces bibliographies employing both manual search techniques and computer searches of on-line data bases; provides reference and loan services; prepares and publishes various materials for use by health science researchers and practitioners; and manages the national on-line information retrieval network. In addition, NLM serves as the Regional Medical Library for the five-state Mid-Atlantic Region and provides back-up services for the national Regional Medical Library Network.

A computerized bibliographic retrieval system was installed in 1964 to help cope with increasing amounts of biomedical literature. This system is known as MEDLARS (Medical Literature Analysis and Retrieval System). In 1971 a refinement of the system became operational and it is now known as MEDLINE (MEDLARS On-Line).

A whole new lexicon has sprung up around the NLM's computerized on-line bibliographic retrieval services: SDILINE, TOXLINE, CANCERLINE, CATLINE, and SERLINE. The most important service for the practicing health professional, however, is MEDLINE.

Briefly, MEDLINE is a system for making accessible a data base of recent journal article references indexed from 3,000 biomedical journals. The references are stored in the Library's computer and are accessible through terminals in approximately 350 hospitals, medical schools, and medical research institutions throughout the country and abroad.

Of special interest to health educators is a collection of health science audiovisuals housed at the National Medical Audiovisual Center in Atlanta, Georgia. The Center which has been part of the Library since 1967, is engaged in developing a program that will have an important influence on health science teaching, recertification, and continuing education programs. With the assistance of panels of medical educators and specialists, the Center is attempting to identify, collect, and evaluate audiovisuals used in medical and dental education. Citation of instructional materials judged to be sound in content and high in technical quality will become part of a new on-line retrieval system known as AVLINE.

Each citation in AVLINE will contain subject headings, an abstract, physical description of the material, identification of intended audience, information on where and how audiovisuals may be obtained, names of principle authors and producers, teaching effectiveness data and a rating of "recommended" or "highly recommended."

The Center also lends health science motion pictures or videotapes to institutions of higher learning and to individual health professionals. The Center anticipates filling in excess of 50,000 requests for film loans during FY 1976.

The Toxicology Information Program (TIP) established in 1966, collects toxicology data from 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 on-line computer searches. Various publications are compiled including annotated bibliographies, directories, and reviews. TIP also functions as the coordinator for toxicology activity for the Department.

The FY 1977 budget request which represents approximately a $6,000,000 increase over the FY 1976 level will allow significant progress to be made in improving basic library services and information transfer capabilities. A major effort will be made to translate new knowledge that is generated and disseminate these findings to the practicing physician.

Medical Library Assistance Program

Authorizing Legislation: Health Services Research, Health Statistics and Medical Libraries Act of 1974.

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Medical Library Assistance Program....	6,333,000	6,433,000	8,000,000	+1,567,000
No. of Awards.....	92	97	135	+38

NLM's programs of Medical Library Assistance are designed to meet the national need for more effective information services. The Act authorizes a number of grant and contract programs to support the training of professional personnel in health information; research in health science information and the application of computer and communications technology; the development of medical reviews and other publications to improve information accessibility; and the improvement of the resources and services of medical libraries. In addition, contracts assist in the development and maintenance of a nationwide coordinated network of Regional Medical Libraries that provide services and resources to medical libraries throughout the United States.

Training grants have supported the education of medical librarians, biomedical communications specialists, and other professionals essential to the health-sciences information system. In recent years the program has concentrated on a new kind of specialist who is able to integrate computer technology into all phases of medicine, including patient care. The major obstacle to progress in the use of computers in medicine has been lack of appropriately trained personnel. By training a core of specialists in the interface between computer technology and biomedicine, NLM hopes to facilitate the application of computers in the medical setting. Fifty-five individuals are presently receiving training in nine programs. There have been twenty-one graduates to date and all are utilizing their computer training in a variety of settings, with the majority on the faculty of medical schools or in teaching hospitals.

Research grants have supported projects in medical library science, information science, biomedical communications systems, and advanced educational technology. One recent study involves ascertaining the preferences of physicians for the various forms of continuing education modalities available to them. The study focuses on the mechanisms and techniques by which a physician learns and/or prefers to learn. Another project is to establish and test a model for retrieval, analysis, and dissemination of medical information utilizing television monitors for immediate feedback. The particular model is transmitting drug information to patient-care areas. The approximate $400,000 increase will be dedicated to two potentially rewarding areas targeted for study in FY 1977. The first is an investigation of the efficacy of using computers in various areas in the health care delivery system. The Review will include an analysis of the computer's potential in the academic and continuing education of all health care professionals, as well as the education of the patient. The second area of interest is research on the mechanisms by which the information is delivered to health professionals and the responsible roles to be played by the National Library of Medicine, the local academic science libraries, and the local hospital libraries in this activity.

Special Scientific Project grants support distinguished health scientists in the full-time analysis of major findings in their respective fields. The studies are published as monographs which make the results of biomedical research widely available. An example is the support of a comprehensive monograph devoted to the discovery, classification, and treatment of infectious diseases and the development of the scientific base for preventive medicine and public health measures to control these diseases. Scientific achievements in microbiology and immunology will emphasize the discovery and classifications of microbes responsible for diseases, mechanisms underlying the causes of illness, and the emergence of the disciplines to further our understanding of these mechanisms.

The Library's publication grants provide support to biomedical scientific publications which would not be profitable projects for commercial publishers to undertake. One recent publication on community medicine synthesizes the manifold experience gained in the diagnosis and solution of community health problems on several continents. The authors of the book are representative of the multi-disciplinary nature of modern comprehensive health care. They seek a rational solution of health problems in the context of all its physical, biological, social, economic, and cultural aspects. The universal usefulness of the study and applicability of the approach to different areas, our own rural problem sectors included, become clearly evident in light of the changes taking place in the health field today. Another project has been responsive to the need for information on the role of women in modern society by supporting a comprehensive bibliography of women in medicine. The bibliography includes approximately 3,500 references to books,articles, reports, and a thesis of scholarly value on the subject.

Medical Library Resource grants assist in the improvement of the nation's health science libraries. The awards are intended to encourage increased financial support for libraries from the hospitals or other institutions that they serve and from the local community. One type of resource grants, the Improvement Grant, traditionally has been a one-year non-renewable grant for up to $3,000 to health institutions, usually hospitals that can demonstrate the need to establish basic collections and services. In FY 1977, this program will expand its support of consortium activities.

In addition to these Improvement Grants, NLM awards resource project grants, which 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 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 ways of expediting 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. In FY 1977, an additional $600,000 will be provided through Resource Grants to upgrade the resources of local libraries within each region.

NLM Library Assistance program provides support for a national network of ten Regional Medical Libraries (RML's). The RML's provide an array of services which have clearly demonstrated that cooperative library 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. The overall demand for loan services has been increasing

at almost 15 percent per year. The RML's through interactive planning with state medical and hospital associations, state library networks and other potential sources for supporting inter-regional information demands can keep Federal support for loans at a reasonable level. The National Library of Medicine serves as back-up resource for the entire RML network. By making available to the RML network its advanced on-line systems, such as MEDLINE, NLM considerably increases the dissemination of research results to all parts of the nation.

Utilization of the network by the health community is expected to increase substantially in FY 1977 for three 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.

Although the RML network has proved itself useful and effective, many isolated health care facilities remain unreached by its services. In FY 1977 NLM will allocate an additional $600,000 to extend RML benefits to smaller and more remote institutions, and on sponsoring cooperative programs. By encouraging cooperative efforts to analyze specific information needs, coordinating acquisition of medical journals, and developing programs for sharing collections, NLM hopes to maximize the dissemination of the latest medical research findings to health professionals.

Lister Hill National Center for Biomedical Communications

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Lister Hill Nat'l Ctr. for Biomedical Communications	2,740,000	2,760,000	4,730,000	+1,970,000
Positions	23	24	23	- 1

The Lister Hill National Center for Biomedical Communications facilitates, through the application of advanced computer and communications technology, the transfer of biomedical information and the sharing of human and physical resources to enhance the effectiveness of health manpower, of health and medical services, and the translation of research results into practice norms.

The activities of the Center fall in the following programmatic areas:

1. Broadband Biomedical Communications
2. Computer-Based Education
3. Computer Technology Research and Development
4. Continuing Education for the Practicing Health Professional
5. Focal Point and Coordination Role, DHEW

1. Broadband Biomedical Communications:

Since July 1,1970, the Lister Hill Center has worked with Dartmouth College and the University of Vermont in planning, building, and helping support the operations of the New Hampshire/Vermont interactive television network known as INTERACT. The experience with this network clearly shows that educational institutions can pool human resources and jointly meet an educational objective which neither can achieve alone. The long-planned phase-out of support by the Center in November, 1975, necessitated the network users assuming total responsibility for its operations.

In a related area, the Lister Hill Center has been engaged in a series of experiments and demonstration projects which apply satellite communications technology to the solution of recognized problems in health education and the delivery of health services. Two satellites in the National Aeronautics and Space Administration (NASA) Application Technology Satellite (ATS) series have been involved, namely ATS-1, which was designed for voice and data transmission, and ATS-6, which provided television images as well. Valuable lessons have been learned from these two major health experiments using satellite-based communications and information exchange systems. The satellite system is highly reliable and avoids most of the interference which plagues conventional high frequency radio communications in Alaska.

In the Alaskan bush, it was possible to extend the services of a hospital-based physician to distant villages by the use of telemedicine conferences supported by a good medical records system. The village-based health aid felt more secure and less isolated; the patients were more confident of the quality of the service received; travel by patients and physicians could be reduced to that which is medically indicated; and the community as a whole improved its understanding of health and the delivery system. The Washington/Alaska/

Montana/Idaho (WAMI) Program demonstrated the possibility inherent in regions' sharing of people and facilities in the medical educational process. The interactive video, audio, and data communications network allowed faculty and students located on multiple campuses and at remote clinical training locations to partake of one coordinated and integrated medical education program.

Continuing this experience and expanding to a national experiment, a program is being planned for the joint Canadian-American Communications Technology Satellite (CTS). The CTS biomedical communications experiment can be divided into three areas of activities. The first is the coordination of program and evaluation planning, technical and engineering supports, and program management for PHS health agencies. The second area of planning involves an expansion of the University of Washington WAMI experiment. The third area is planning for facilities within the National Library of Medicine to provide the staff of the Lister Hill Center with a temporary laboratory. Although this laboratory lacks the sophistication that will be available in the new Lister Hill Center Building it offers an opportunity to make a small beginning in video experiments and demonstrations. This will enable the Center's communications engineering staff to explore advanced technology as a medium for extending effective educational programs to the health community; for improving health care delivery; and for enabling more effective dissemination of research results.

2. Computer-Based Education:

The current year is the terminal year of a project to foster the interinstitutional sharing of computer assisted instruction (CAI) resources among medical schools, hospitals, and other health related organizations.

One of the current activities which holds great promise is the development within the National Library of Medicine of a training laboratory designed to consolidate computer-based educational resources in a single area. This learning laboratory will be the place where potential users can gain an operational understanding of the many alternative modes available to the generator and sponsor of programs in computer assisted instruction (CAI). The laboratory will permit the staff to be active participants in selected experimental projects, and thus become a focus for the entire health community.

Another major objective of the Center is to facilitate educational activities which are designed to preserve professional competence through postgraduate education. As a part of this effort, the Center's Computer Technology Branch is planning collaborative projects with the Association of American Medical Colleges (AAMC) so that the expanding body of computer-based educational materials can be reviewed, organized, and regulated to conform to orderly library procedures.

3. Computer Technology Research and Development:

The cost of large host computers needed by many current CAI and library applications programs is a significant deterrent to expanded use of these programs. The Center's computer technology staff is investigating the potential for using smaller and less expensive computers, i.e., minicomputers, to make available substantial computer power to a large number of widely dispersed users at affordable costs. However, the more widespread use of minicomputers will aggravate a problem which is already serious. Computer-based education programs cannot be shared readily because they are written in many languages and dialects. The Center is actively supporting language standardization so that existing and future clinical programs can find greater use, especially in the continuing education of health professionals.

Using the new technology laboratory in the Library, the staff is examaning how best to provide more effective and efficient user access to computers through the use of interactive terminals. This examination includes several advanced terminals, terminal configurations, and terminal functions. The full potential of such laboratory experiments cannot be fully realized until specially designed space is available in the new Lister Hill Center Building.

4. Activities in Continuing Education for the Practicing Health Professional:

There exists a vast array of educational opportunities in continuing medical education (CME) having varied sponsorship and effectiveness. There also exists a disturbing sense that current efforts are relatively ineffectual, inefficient, or of less than desirable quality or applicability. It is recognized that the benefits of biomedical research results become reflected in the accepted norms of health professional practice through the process of effective and efficient biomedical communications. This important process is in need of considerable improvement if it is to become a significant factor in CME, including conventional programs designed to maintain professional competence of the practitioner.

In the practice arena, the information which is disseminated must be analyzed for its accuracy and relevance to clinical problems, must be snythesized from the total biomedical information pool, and must be translated into a language and format which is understood by the practitioner. The Center is emphasizing the development of strategies in analysis, synthesis and translation as a new approach for improving continuing medical education activities. A specific effort involves collaborative planning with the Health Services Administration (HSA) and the Health Resources Administration (HRA) with the goal of developing an information-consultation-education program for physicians in rural areas, especially physicians serving in the National Health Service Corps.

5. Focal Point and Coordination Role:

The Center has assumed an active coordination and technical support role in two broad areas. The first is to undertake planning, experimentation, and evaluation programs which will lead to the development of a coordinated plan for a broadband biomedical communications network responsive to the current and evolving needs of the health agencies. This activity is planned for accomplishment during the next three years, and will require correlating evaluation of experimental results with requirements studies and technical systems options to result eventually in a proposed design for a national network. The second area is the development within the National Library of Medicine, temporary laboratory capabilities for exploring the potential communication and computer technologies.

6. Dissemination of Research Results:

The approximate $2,000,000 increase for the Center will enhance its efforts to improve the effectiveness and efficiency of biomedical communications and improve the dissemination of research results. Primary efforts will be targeted at developing new and improved uses of technology for scientist to practitioner communications. The Center's expertise in telecommunications and satellite communications offers a unique opportunity for televised clinical conferences, demonstration and staff seminars between NIH and other centers within the biomedical community. These same communication links will be developed for improving continuing medical education, public education, and remote patient presentation and diagnosis.

National Medical Audiovisual Center

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
National Medical Audio-visual Center.....	3,096,000	2,981,000	3,551,000	+570,000
Positions.....	100	100	100	---

The National Library of Medicine and the Bureau of Health Manpower, HEW, have been carrying out a joint program now known as the Learning Resources Program to improve the use and effectiveness of learning materials in health sciences schools. NMAC and Bureau activities include research, audiovisual development, evaluation, distribution, training, consultation and related assistance to medical institutions through grants, demonstrations, contracts, and direct programs.

Advances in educational technology in the last 15 years have provided a solid base for transforming health science education and making it more responsive to the needs of students and practitioners. Recent approaches to education stress the benefits of the learner developing performance skills during training instead of the teacher traditionally "covering" course content. They emphasize that instructional programs should be tested and revised until each can consistently teach skills required for professional performance. Incorporation of these principles into learning programs which make full use of the capabilities of modern audiovisual media systems is the central goal of the National Medical Audiovisual Center in Atlanta, Georgia.

Audiovisual technology can promote significant changes in the training of health professionals. Where the need is to recognize learning styles and for customized learning programs to make instruction more suitable and effective for individuals, then audiovisual educational technology can provide the necessary spaces, instructional media and other resources. In individualized programs, students will have greater flexibility in scheduling their learning experiences. It will become increasingly possible for students to assume responsibility for their own learning, both in undergraduate training and throughout their professional careers. Validated criteria and learning competencies for health careers will enable the student to check on his progress and measure his professional growth. Research, development and training in these areas will lead to more effective health sciences education and better trained health professionals.

Center-supported peer review panels evaluate health science teaching materials. This on-going review process provides input for the Library's data base on audiovisuals known as AVLINE. The AVLINE system is designed to provide quick access to comprehensive information on biomedical audiovisuals in much the same way that NLM's MEDLINE system does for printed materials. Since 1971, 51 panels have reviewed 6,000 educational items, and found 3,600 suitable for inclusion in AVLINE. These materials are acquired for reference and direct loan or duplication to schools for their use. In 1977, it is estimated that approximately 1,200 materials will be found suitable for inclusion into AVLINE.

NMAC has launched an organized program of research and evaluation to develop, implement, and measure the effectiveness of programs using audiovisual media and educational methodology in health sciences education. The Center

is planning to establish a regional focal point to accomplish the design, development, testing and evaluation of teaching approaches and strategies through cooperative effort of regional faculty and institutional resources. Studies on materials design, descriptive reviews of curricula, and development of audio-visual systems and production techniques are currently planned. Concepts and information coming from studies are used in instructional development and training programs assisting health professional faculty in improving instruction. In FY 1976, the Center's training program attracted more than 500 participants and is expected to increase to 640 in FY 1977.

The approximate $600,000 increase in the program's FY 1977 funding level will modestly expand the acquisition and clearinghouse functions and other basic services of the Center. Preliminary developmental efforts will continue on the bibliographic information retrieval system AVLINE (Audiovisuals on-line). The utilization of the NLM's computerized nationwide information network in this manner acts as an offset to the nation's health manpower shortage by increasing the effective use of technology in the health education process.

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Library Operations

	1976 Revised President's Budget	1976 Appropriation	1977 Estimate	Increase or Decrease
	Amount	Amount	Amount	Amount
Library Operations.....	10,169,000	10,014,000	10,993,000	+979,000
Positions.....	250	252	250	- 2

Library Operations, the service arm of the National Library of Medicine providing both traditional and innovative services, is responsible for selecting, acquiring, indexing, processing, cataloging, preserving, and disseminating the world's output of substantive biomedical literature. In carrying out these responsibilities, Library Operations has developed rapidly expanding activities and services for the benefit of the entire biomedical community. It provides access to the Library's resource material through the utilization of advanced bibliographic retrieval services and a national on-line information retrieval network. (MEDLINE)

Even as service workloads and the volume of literature increase, Library Operations estimates that it will keep abreast of its FY 1976 level of service operations; acquiring 140,000 serial pieces and 20,000 monographs; indexing 245,000 biomedical articles for inclusion in the computerized MEDLARS data base; publishing 32 recurring bibliographies, binding 32,000 volumes and processing approximately 250,000 interlibrary loan requests; processing 100,000 reader service requests; and delivering 500,000 on-line searches and two million pages of bibliographic citations from on-line searches.

In FY 1975-76 the NLM installed a greatly improved successor to its Medical Literature Analysis and Retrieval System (MEDLARS), which provides the machine-readable data base for its publications and bibliographic search programs. This second generation system, known as MEDLARS II, enabled NLM to develop new and specialized services based on the system's greatly expanded capabilities, including the extension of MEDLINE and other on-line services to hospitals, pharmaceutical and other industrial educational organizations. The on-line network will be further expanded in FY 1977, providing access to many smaller hospitals and community-based academic institutions with preclinical and paramedical training programs. One of the newer capabilities has permitted the inclusion and searching of abstracts of articles in the MEDLARS II on-line data bases. In FY 1977 the number of author abstracts will exceed 100,000 abstracts from the most important journals, thus further augmenting the usefulness of MEDLINE and other NLM on-line data bases to the health sciences community.

During the past year an experimental referral system, DOCLINE (Document Delivery On-Line), for interlibrary loans was initiated. DOCLINE has developed successfully into a computer-based interlibrary loan verification, routing, and management information system. Based on this experience, the Library is preparing to extend this pilot experiment to the Regional Medical Library Network. DOCLINE will interface with the NLM's successful systems SERLINE (Serial Locator File) and CATLINE (A file of catalog data).

In order to optimize access to resources for the medical library community Library Operations has devoted a significant portion of its resources to participation in cooperative programs with the Library of Congress, the

Ohio College Library Center, the State University of New York. During the next year Library Operations will play an active role in developing and improving its on-line systems capabilities. Requirements in shared-cataloging utilizing production of catalog card sets in individualized format also will be tested. It is expected that the cooperating libraries will begin inputting their bibliographic records for serials and monographs into the OCLC system during 1977.

Major projects receiving allocations from the approximate $1,000,000 increase in Library Operations will have as their goal the transfer of more current information in more suitable formats to the ultimate users of the Library's resources. More author abstracts will be added to the MEDLINE data base to allow MEDLINE users to improve the process of selecting only those articles which are timely and subject matter relevant. The program will initiate efforts to integrate DOCLINE with the existing bibliographic retrieval system of the Regional Medical Libraries. This effort will permit more rapid throughput time for interlibrary loan requests. Steps will be taken to initiate a service based on the MEDLARS capability to store profiles of users information needs. The services known as Selective Dissemination of Information (SDILINE) will be provided to majro medical schools and hospitals and will furnish literature on the most recent advances in health care and health research to thousands of practitioners.

Toxicology Information Program

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Toxicology Information Program	1,873,000	1,866,000	2,166,000	+300,000
Positions	16	17	16	-1

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 files of governmental, industrial, and academic organizations in whatever form it is available. This information is then organized and entered into computerized storage and retrieval systems for the purpose of developing systems and services to make results of toxicological investigations more readily available to those who make therapeutic decisions, conduct research, make regulatory decisions, and monitor the environment.

ON-LINE SYSTEMS

The TIP utilizes on-line information retrieval technology to make toxicology information more readily available to members of the biomedical community. During FY 1976, TIP continued to expand its bibliographic retrieval service (TOXLINE) which was operated entirely on the NLM computer. The data base also was enriched with special literature files to improve coverage in the specific areas of mutagenesis, teratology, and heavy metal toxicology.

The usefulness of the service was enhanced by updating the TOXLINE data base on a regular monthly (instead of quarterly) basis. The growth of the data base to over 400,000 records required a splitting of the file into two parts, TOXLINE and TOXBACK. TOXBACK contains that portion of the data base covering the literature prior to 1971, and is only searchable off-line. TOXLINE contains literature published during the most current five years and is available on-line. During this period, users performed over 25,000 on-line searches and requested over 250,000 pages of off-line print. Provisions have also been made to allow TOXLINE access by foreign MEDLARS centers.

During FY 1976, TIP continued to operate and enhance its Chemical Dictionary On-Line (CHEMLINE). This service is an adjunct to TOXLINE, MEDLINE, and CANCERLINE and provides users with Chemical Abstracts Service (CAS) Registry numbers and chemical nomenclature information for substances mentioned in these files. Some 15,000 chemical substance records have been added to the file bringing the total size of CHEMLINE to 90,000 records. Data for an additional 700-1,000 chemical substances will be added to the on-line data retrieval service, the Toxicology Data Bank (TDB). Support functions for TDB users such as training and technical assistance will be maintained.

An initial file of 700 compound records for a new on-line data retrieval service referred to as the Toxicology Data Bank was mounted in NLM's on-line system. The file is being developed and maintained by extracting data on the chemical, physical, biological, usage and distribution attributes of compounds from a selected group of sources such as monographs, reviews and criteria documents. Compounds are chosen for input if they present known hazards to substantial population groups.

TIP will continue to enrich TOXLINE with specialized literature files covering areas such as drug interactions, drug interference with laboratory tests, and biological aspects of drug abuse. TOXLINE will be updated on a regular basis, and the oldest year of the file will be transferred to TOXBACK on an annual basis.

COLLABORATIVE ACTIVITIES WITH OTHER ORGANIZATIONS

The Toxicology Information Subcommittee (TIS) of the DHEW Committee to Coordinate Toxicology and Related Programs, which is responsible for coordinating toxicology information activity within and beyond the Department, is making significant progress on three major projects intended to improve the information transfer process. The National Library of Medicine, through its TIP, has been assigned operational responsibility for the Toxicology Information Subcommittee which was formally chartered by the Office of the Assistant Secretary for Health in 1973. These collaborative efforts include:

The TIP-supported Toxicology Information Response Center (TIRC) at the Oak Ridge National Laboratory continued to fill an important need for query response and literature search services in toxicology. This Center, which performs demand literature searches has processed over 700 searches in FY 1976 for the scientific community. Search results normally consist of computer print-outs containing bibliographic references and abstracts from on-line computer searches, copies of abstracts extracted from Chemical Abstracts, Biological Abstracts or other services, and typed citations of relevant articles. During FY 1976 this literature support service was provided to other Federal agencies including the National Center for Toxicological Research, Edgewood Arsenal, Food and Drug Administration, EPA, etc. via separate Interagency Agreements.

The Laboratory Animal Data Bank (LADB) project which is designed to make base line data on laboratory animals available, on-line, to research scientists. This data bank will contain strain files for most species of laboratory animals. Each strain is represented by a number of colonies (substrains). The species included will range from mice to primate. Data collected is related to environmental and handling conditions under which each colony is maintained; also in such areas as blood chemistry, growth and development, behavior, and pathology. The data is stored for on-line retrieval and statistical manipulation. The initial segment of this file was placed on-line for test and demonstration purposes. This segment is a file on 10 key (mice, rats, beagles and Rhesus monkeys) strains.

An information center, known as the Toxicology Document and Data Depository (TDD), has begun collecting and distributing toxicology materials not ordinarily published in professional journals. Materials such as "negative" research results, data files, charts and photomicrographs, hearing transcripts, and committee reports will be included. This information will be on microfiche and distributed by the National Technical Information Service under an interagency agreement with NLM.

The approximate $300,000 increase in funds will allow TIP to expand TOXLINE, CHEMLINE and the Toxicology Data Bank. In particular the program will develop an on-line "early warning" system on the potential hazards of products about to enter the market place. In addition TIP will take steps to make TIRC at Oak Ridge more sophisticated and versatile with increased use of machine search techniques and access to all available on-line files relevant to toxicology.

Program Management

	1976 Revised President's Budget Amount	1976 Appropriation Amount	1977 Estimate Amount	Increase or Decrease Amount
Program Management.....	5,245,000	5,190,000	5,794,000	+604,000
Positions.....	79	79	79	---

This activity provides support for the overall administration, coordination, and direction of the varied programs and activities of the National Library of Medicine. Within this activity the primary functions include the preparation and processing of grant applications for review committees and NLM's Board of Regents; public information and publication management; financial and personnel management; program analysis and contracts management; administrative services, and coordination of NLM's equal employment opportunity activities.

This activity includes a major effort, the architectural and engineering design of the Lister Hill Center, which was completed in July of 1975. This facility when constructed will relieve the serious space shortage within the NLM and provide the necessary special purpose facilities essential to meet the needs of the Lister Hill Center programs' communications technology and network engineering activities.

Also in 1976, Program Management performed detailed analyses of NLM computer and library services in order to optimize efficiency in these operations. As a means of analyzing work volume in relation to manpower utilized to perform that work, a productivity measurement system was developed and is tracking library services on a monthly basis.

This activity will continue to emphasize introduction of new knowledge into current operating programs and for planning and review of new areas of focus and interest.

The entire increase for this activity in this budget is required for mandatory items which include the annualization cost of recent pay increases and NLM's proportionate share of increased costs of NIH centrally furnished services such as maintenance of building and grounds, custodial services, communications and administrative services.

workers in all fields and in all geographic areas can avail themselves of the benefits of the network; and (4) the greater and more direct involvement of the health professionals themselves not only from the standpoint of decision making in the library areas, but also in the continued identification of information needs, in the design of programs which require information components and in the communication linkages of a national Biomedical Communications Network.

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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
24	2,760,000	Indefinite	23	4,730,000

Purpose: The Lister Hill Center facilitates, through the use of advanced computer and communications technology, the transfer of biomedical information and the interinstitutional sharing of resources to enhance the effectiveness of health manpower, of health and medical services, and the transfer of research results into practice norms.

Explanation: The Center works closely with the health and medical community to determine high priority needs, and matches these needs with technological capabilities in order to develop experimental programs and evaluate their feasibility.

Accomplishments in FY 1976: With the move of the ATS-6 satellite to India, the Center terminated its highly successful experiments with the Alaska biomedical communications network for remote health care delivery and with the state of Washington in its program for decentralized medical education. Expanding on this base, the Center is now planning a major national broadband network experiment using the joint Canadian-American Communications Technology Satellite (CTS).

The Lister Hill Center terminated its support of the experimental computer-assisted instruction (CAI) network as planned on May 30, 1975. Also, the Center's support for the New Hampshire/Vermont interactive television network (INTERACT) essentially terminated on November 30, 1975. The management and operation of both of these networks has been assumed by their respective users with the anticipation that they will be self-sustaining.

In the area of computer-based education, a major effort is underway to develop a Learning Resources Center within the National Library of Medicine. This will provide a focal point for institutional representatives to access all computer-based education modalities. Additionally, it provides a temporary laboratory for developing advanced applications of small computers and interactive terminals for both computer-based education and library applications.

Objectives for FY 1977: There are five broad areas in which the Center will take initiatives during FY 1977. A BROADBAND BIOMEDICAL COMMUNICATIONS NETWORK will be the foundation on which much of the resource sharing will be based. The CTS experiment complements a study which will be conducted by the Center and the National Aeronautics and Space Administration (NASA) to explore the potential use of satellite communications in support of health. This study will be the base on which to develop models and system designs for a national broadband biomedical communications network. The

network could eventually support all communications and information transfer modes. DISTRIBUTED COMPUTER PROCESSING will make available at reasonable costs the power of the computer to support library activities, computer-based education, and medical practice in isolated locations. Research and development in distributed processing will be intensified during FY 1977 to minimize dependency on large central computer systems. ALTERNATIVE TECHNOLOGIES will be examined to provide options from which applications can be selected to best meet a particular set of requirements of an individual user. Efforts will continue to develop a strong in-house research development, demonstration, experimentation, and evaluation capability. Development of TRANSLATION METHODOLOGIES is essential if the benefits of research are to be understood and applied by practitioners in a timely fashion. The Center will undertake a systematic examination of the parameters of the translation of research results to practice application. INFORMATION ACQUISITION AND EXCHANGE will promote current awareness on the part of the Center as it consults with its constituency in the health community in seeking the best technology for application to specific communication problems. An information base and methodology for maintaining its currency will be developed to provide up-to-date information on basic technology and its applications. The Center will maximize the DISSEMINATION OF RESEARCH RESULTS and medical research findings to health professionals.

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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
100	2,981,000	Indefinite	100	3,551,000

Purpose: The National Medical Audiovisual Center (NMAC) located in Atlanta, Georgia applies audiovisual technology to the instructional needs of the biomedical community. Its primary mission is to stimulate the development and use of instructional media 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 material. It evaluates, acquires and distributes materials appropriate for health professional education, and provides consultation and training in the use of instructional audiovisual technology. It also conducts research in instructional technology and systems and develops prototype instructional media programs.

Accomplishments in FY 1976: NMAC implemented its on-line bibliographic storage and retrieval system, AVLINE (Audiovisuals on-line). 65,000 films, videotapes and videocassette instructional programs were loaned to health professional schools. In 16 workship sessions, over 500 health science professionals were trained in methods of application of audiovisual educational technology to health sciences teaching. NMAC suggested or developed teaching materials in the areas of dentistry, anatomy, nursing,physiology and neurology. In addition, an active research and evaluation program in instructional technology and its application to audiovisual systems and instructional applications was initiated.

Objectives for FY 1977: NMAC will continue to identify areas for research, development and services where audiovisual technology can, when properly applied, promote significant changes in the effectiveness of health professional training. Center-supported peer review panels will continue to identify additional effective materials for entering into the AVLINE system, an on-line system which will assist health science teaching professionals in identifying instructional materials for use in health professional schools. By the end of FY 1977 an additional 3,000 audiovisual citations will have been added to the AVLINE file. NMAC will continue its services to the health professional community through direct loans of films, videotapes and videocassettes,through adding materials for sale through the General Services Administration's Sales Program, and by continuing a training program which increases health professional faculty competencies in development and use of materials designed to improve student performance. A number of demonstration instructional slide series, videotape and audiotape programs will be produced in FY 1977 primarily as part of NMAC's research and development programs.

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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
252	10,014,000	Indefinite	250	10,993,000

Purpose: Library Operations is responsible for selecting, acquiring, processing, indexing, cataloging, preserving, and disseminating the world's output of substantive 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. In carrying out these responsibilities, Library Operations functions as the traditional service arm of the National Library of Medicine.

Explanation: Library Operations, through manual and machine methods prepares bibliographies and publishes indexes, catalogs, and other publications for use by the biomedical community; manages a national on-line information retrieval network, and conducts an extensive educational program for its network participants.

Accomplishments in FY 1976: Library Operations continued to expand the on-line service provided to the health community during FY 1976. At the beginning of FY 1976, the program was providing service to approximately 350 institutions and is expected to grow to 500 during FY 1977.

The Library acquired 140,000 biomedical serial pieces and 20,000 monographs; indexed 245,000 biomedical articles to be entered into the computerized MEDLARS data base; published 32 Recurring Bibliographies; bound 32,000 volumes; and processed approximately 250,000 interlibrary loan requests; filled 100,000 reader service requests; and produced two million pages of bibliographic citations from 500,000 on-line searches.

NLM's second-generation computerized Medical Literature Analysis and Retrieval system (MEDLARS II) was installed in FY 1975. A sophisticated successor to the older MEDLARS system in operation since 1963, the new system has made possible the development of additional bibliographic information services, and permitted the extension of MEDLINE and other on-line data bases to industrial, pharmaceutical and other health related institutions.

NLM renewed agreements with eight international MEDLARS centers which have been providing NLM with quid pro quo indexing of the foreign literature. These new agreements reflect the new capabilities which the MEDLARS II system provides such as on-line access and additional data bases.

Objectives for FY 1977: Services provided by Library Operations in response to a steadily rising demand will experience a considerable increase. For instance, in FY 1977 requests for library loans alone increased by 27 percent. Current projections foresee a rise of 25 percent for the next two years. Expressed in numbers, 71,000 more loan requests will be processed. Based on current productivity levels this increase represents 8.7 man-years.

A major objective in FY 1977 will be to increase the responsiveness of the NLM and its Regional Medical Library Network to this existing service demand. To this effect, Library Operations has designed an on-line interlibrary loan referral system, DOCLINE, which has been operational on an experimental basis between the British Library Lending Division (BLLD) and the NLM since 1974. It is anticipated that by FY 1977 a significant portion of interlibrary loan requests as well as referrals to the National Library of Medicine will be automatically controlled by DOCLINE. An essential aspect of this service will be an integrated management information system. By applying computer technology to document delivery in the same way in which MEDLINE and other on-line services of the NLM have applied it to information retrieval, NLM is responding to the needs of the health science community.

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)

1976		1977		
			Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
17	1,866,000	Indefinite	16	2,166,000

Purpose: The Toxicology Information Program (TIP) is responsible for collecting and organizing toxicology data from diverse sources and making it more readily accessible to the biomedical community.

Explanation: TIP obtains information from the published scientific literature and files of governmental, industrial, and academic organizations in whatever form it is available; organizes and enters this information into computerized storage and retrieval systems; and provides specialized services and products. TIP plays a key role in coordinating toxicology information activities within DHEW.

Accomplishments in FY 1976: TIP continued to expand its bibliographic retrieval service (TOXLINE) which was operated entirely on the NLM computer. The data base was enriched with special literature files to improve coverage in the specific areas of mutagenesis, teratology, and heavy metal toxicology. A major improvement was made to the usefulness of the service by updating the TOXLINE data base on a monthly basis. The data base grew to over 400,000 records. Users have performed over 25,000 on-line searches and requested over 250,000 pages of off-line print.

TIP continued to operate and enhance its on-line Chemical Dictionary (CHEMLINE). Some 15,000 chemical substance records have been added to this file bringing its total size to 90,000 records.

A new on-line data retrieval service referred to as the Toxicology Data Bank was mounted in NLM's on-line system. The initial file of 700 compound records contained extensive data on substances known to be hazardous to substantial population groups.

CANCERLINE, an on-line file containing bibliographic information on cancer, was maintained for the National Cancer Institute. A file describing on-going cancer research projects (CANCERPROJ) was added as a new subset of this service.

TIP supported the Toxicology Information Response Center at the Oak Ridge National Laboratory where query response and literature search services in toxicology were carried out on a demand basis. During the year over 700 full bibliographic searches were processed.

Objectives for FY 1977: TIP will continue to enrich TOXLINE with specialized literature files covering selected areas such as drug interactions, drug interference with laboratory tests, biological aspects of drug abuse, etc. The TOXLINE data base will be updated on a regular monthly basis, with the oldest year of the file transferred to TOXBACK on an annual basis. TOXLINE will be modified to include an "early warning" system on the potential hazards of products about to enter the market place. The CHEMLINE file will be maintained and improved. New software enhancements will enable users to increase on-line sub-structure searching capabilities. Data for 700-1,000 chemical substances will be added to the Toxicology Data Bank. As part of its expanded chemical file support services, a study will be conducted to determine the feasibility of creating an "agency" chemical registry system for the NIH.

Plans for FY 1977 call for increased query response services from the Toxicology Information Response Center with the sale of selected search bibliographies through the National Technical Information Service. Steps will be taken to make TIRC more sophisticated and versatile with increased use of machine search techniques and access to all available on-line files relevant to toxicology.

NATIONAL INSTITUTES OF HEALTH

National Library of Medicine

Program Purpose and Accomplishments

Activity: Program Management (Public Health Service Act, Title III, Part I, Sec. 381)

1976		1977		
Pos.	Amount	Authorization	Budget Pos.	Estimate Amount
79	5,190,000	Indefinite	79	5,794,000

Explanation: This program provides support for the Office of the Director, which has responsibility for overall administrative management and scientific direction of all NLM programs.

Purpose: This activity provides the funds for salaries and other related operating costs for the overall administration and direction of the National Library of Medicine programs.

Accomplishments in FY 1976: NLM grants awarded and administered under the Medical Library Assistance Act were continued to be analyzed and evaluated through an on-line computerized system. The final architectural and engineering drawings for the new Lister Hill National Center building were completed. The construction of this specialized facility will allow NLM to apply advanced technology to the improvement of biomedical communications.

Objectives for FY 1977: The activity will continue to provide for the coordination and administration of NLM programs. Particular emphasis is to be directed in the areas of new knowledge, and its evaluation and applicability relative to the methods and systems necessary for the dissemination of medical research results.

Transition Quarter Analysis

Obligations by Activity

	1976		Interim Period	
	Pos.	Estimate	Pos.	Estimate
Medical Library Assistance				
Total	---	6,433,000	---	870,000
Direct Operations				
Lister Hill Nat'l Center for Biomedical Communications	24	2,760,000	23	665,000
National Medical Audiovisual Center	100	2,981,000	100	745,000
Library Operations	252	10,014,000	250	2,610,000
Toxicology Information	17	1,866,000	16	475,000
Program Management	79	5,190,000	79	1,207,000
Subtotal	472	22,811,000	468	5,702,000
Total Obligations	472	29,244,000	468	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.

OFFICE OF THE DIRECTOR AND BUILDINGS AND FACILITIES

WITNESSES

LEON M. SCHWARTZ, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NATIONAL INSTITUTES OF HEALTH
DR. DONALD S. FREDRICKSON, 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
NORMAN D. MANSFIELD, DIRECTOR OF FINANCIAL MANAGEMENT, NATIONAL INSTITUTES OF HEALTH
B. F. GARDNER, JR., CHIEF, BUDGET PRESENTATION AND COORDINATION BRANCH, DIVISION OF FINANCIAL MANGEMENT, NATIONAL INSTITUTES OF HEALTH
JACK GLASS, BUDGET OFFICER, OFFICE OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH
ROBERT B. LAUDER, JR., BUDGET OFFICER, DIVISION OF ENGINEERING SERVICES, NATIONAL INSTITUTES OF HEALTH
CHARLES MILLER, DEPUTY ASSISTANT SECRETARY, COMPTROLLER

Mr. NATCHER. We take up next the Office of the Director and buildings and facilities.

Dr. Fredrickson, who will justify this request?

Dr. FREDRICKSON. Mr. Schwartz.

[Mr. Schwartz' biographical sketch follows:]

Name: Leon M. Schwartz.
Postion: Associate Director for Administration, NIH.
Birthplace and date: Baltimore, April 26, 1928.
Education: A.B., Economics, John 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 Administration, Office of Education, DHEW, 1967–68; Goddard Space Flight Center, National Aerouautics and Space Administration, 1960–67; Chief of Program Review and Resources Management, 1966–67; Director of Program Support Division, 1965–66; business manager, meteorology 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 memberships: Maryland Association of Certified Public Accountants; memberships: 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.

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OFFICE OF THE DIRECTOR AND BUILDING AND FACILITIES

Mr. NATCHER. Mr. Schwartz, I believe you are the Associate Director for Administration, National Institutes of Health. We are delighted to have you with us today.

Who do you have with you?

Mr. SCHWARTZ. Thank you, Mr. Chairman. We are delighted to be here.

With me to my immediate left is Ross Holliday, the Director, Division of Engineering Services; and if you don't mind I would like to introduce some of our budget people. We have Jack Glass, Bob Lauder, and Mary Parker.

Mr. NATCHER. Fine. We are delighted to have all of you folks with us at this time.

Mr. Schwartz, we have had occasion to examine your statement. You have an excellent statement. With your permission we would like to insert it in the record in its entirety at this point and go directly to the questions.

Mr. SCHWARTZ. Thank you, sir.

[The statement follows:]

Mr. Chairman and members of the committee, the office of the director appropriation provides for the central executive direction and management of the various programs, as well as provision of some essential services, of the National Institutes of Health. Specifically, this appropriation includes:

(1) The Director and his immediate staff and the offices responsible for program planning and evaluation and public and scientific communications; and

(2) 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 and division directors and their supporting staff.

PROGRAM MANAGEMENT

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.

PROGRAM SERVICES

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 number of management and program services on a consolidated central basis. The central 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, activities to assure equal employment opportunities, and a wide range of other personnel management services for over 11,000 employees; contracts and grants management services relating to approximately 24,000 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 has also assumed overall leadership in carrying out congressionally mandated responsibilities such as dissemination of research results, and fulfilling the requirements of the Freedom of Information and Privacy Acts.

APPROPRIATION REQUEST

Mr. Chairman, the appropriation request for the office of the director is $16,234,000 for 1977, an increase of $909,000 over the 1976 level of $15,325,000, a comparative amount which reflects the transfer of the standard level user payments to the Bureaus, Institutes, and Divisions of the National Institutes of Health to provide for a more equitable distribution of rental costs. The requested increase of $909,000 is entirely attributable to mandatory costs—that is, within-grade increases, annualization of the 1976 pay increases, increased postage rates, increased payments to the NIH management fund, and the like.

BUILDINGS AND FACILITIES

The Buildings and Facilities appropriation provides funds for design, construction, repair and improvement of facilities for the National Institutes of Health.

In total, we are requesting $25,400,000 in fiscal year 1977 for the following:

Ambulatory care facility	$21,700,000
Repairs and Improvements—plant	1,000,000
Repairs and improvements—program	2,000,000
Master utilities extension	500,000
Potable water systems	200,000

I will discuss each of these briefly.

AMBULATORY CARE FACILITY

1977 BUDGET REQUEST $21,700,000

These funds are requested to permit construction to begin on the ambulatory care research facility which is to be a major addition to the clinical center, to be constructed on a site adjacent to the north face of the existing building. The need for this facility is considered to be of the highest priority among the several projects being planned for construction by NIH. The facility is needed to support an increase in emphasis in translating basic research results to health care by enlarging outpatient clinical programs. In addition, the project will provide for modernization of outmoded clinical departments in the existing clinical center such as surgery, intensive care, pathology, and diagnostic radiology.

Design funds for the project in the amount of $3,580,000 were provided in fiscal year 1973. The design is about 30 percent completed. The construction is estimated to cost about $95 million including the building, parking, and renovations to the existing clinical center bulding. The funds requested in the amount of $21,700,000 in fiscal year 1977 will support the cost of the first phase of construction.

REPAIRS AND IMPROVEMENTS—PLANT

1977 BUDGET REQUEST $1,000,000

These funds are needed to continue the program of major repairs and improvements to the physical plants at Bethesda, Md.; Poolesville, Md.; Hamilton, Mont.; Baltimore, Md.; and other field stations for which NIH has the real property holding agency responsibility. As you know, the plants are quite extensive and many of the buildings and facilities have been in service between 35 and 40 years. This is a continuing need of providing for the care and upgrading of the various mechanical, electrical, and structural systems.

REPAIRS AND IMPROVEMENTS—PROGRAM

1977 BUDGET REQUEST $2 MILLION

These funds are also required 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. Prior to 1975, funding of this work had been provided from the operating appropriations of the Institutes. The work includes changes in physical facilities to accomodate revisions and new initiatives in research efforts.

MASTER UTILITIES EXTENSION

1977 BUDGET REQUEST $500,000

The funds requested in fiscal year 1977 are needed for the extension of communication and other miscellaneous utility systems. This project encompasses all NIH utility systems. An addition to the air-conditioning plant is currently being designed. Construction is expected to start in early fiscal year 1977.

POTABLE WATER SYSTEMS

1977 BUDGET REQUEST $200,000

In 1977, $200,000 is requested for the first phase of a two-phase project needed to protect the potable (drinkable) water systems in the clinical center. This project will provide two separate water systems, one for patient care areas and the second for laboratory areas, to prevent cross-contamination between the water systems of these two areas.

The first phase of the work will also include preliminary engineering development and definition of the scope of the second phase, which is roughly estimated at this time to be about $500,000. The work is being scheduled in two phases to reduce disruption to research and patient care areas.

Thank you. I shall be happy to respond to any questions you may have.

CONSTRUCTION OF FACILITIES

Mr. NATCHER. I want to ask you about the $54 million we gave you for last year for construction of two buildings until the transition period. Could you describe to this committee your timetable for completion of these projects and any special problems which you have developed?

Mr. SCHWARTZ. I will cover for you, sir, some of the highlights, and then I can put all the details into the record.

Mr. NATCHER. That will be fine.

Mr. SCHWARTZ. With the Lister Hill Center we have completed the design, and at this point we have only one additional step, and that is the filing of our environmental impact statement. We expect to issue the draft environmental impact statement for review by the public in about 30 days. The review period will be 45 days. It goes through the A–95 review at the State level. Also local governments and citizen associations and others will review and provide comments. At the end of that 45-day period we expect to take about 30 days to incorporate and respond to the comments and then to deliver the statement to the Council on Environmental Quality. This requires a 30-day wait with the Council.

So assuming that this process goes through as we envision it, we will be ready to advertise the project and award a contract during the month of the transition quarter.

The other large obligation during that period of time is for the Environmental Health Facility in North Carolina. We are at about the same point. The design is 90 percent complete. We are also completing our environmental impact statement, and we have a process quite similar to Lister Hill to go through.

So the two projects are running pretty close together, and we expect to have both obligated during the transition quarter. The Lister Hill Center construction is estimated to be completed in about 30 months after award of the contract. The Environmental Health Facility will require a similar period for construction following award of the second phase construction.

Mr. NATCHER. Mr. Schwartz, you are not requesting funds for the remaining construction phases of the National Institute of Environmental Health Sciences Building. Why is that? Don't you need the money to award contracts during fiscal year 1977?

Mr. SCHWARTZ. The appropriation bill which contained the authority to initiate the project had not been law at the time we went through the development of this budget, so, therefore, it was not considered as a fiscal year 1977 item. However, as Dr. Rall testified this morning, this will have a very high priority during the development of the fiscal year 1978 proposal.

I will report to you, however, that if funds are available during fiscal year 1977, we will be able to go ahead with the second phase of the environmental health facility and perhaps save some funds that were attributed to the cost of inflation and delay of construction projects.

AMBULATORY CARE RESEARCH FACILITY

Mr. NATCHER. Mr. Schwartz, turning to your current request, can you explain in more detail why the clinical center needs a separate outpatient facility?

Mr. SCHWARTZ. Mr. Natcher, I am very happy to have at the table Dr. Fredrickson who worked for many years within the clinical program at NIH, and since he has been Director of NIH has spent a great deal of time looking at this project and how it relates to the total intramural program.

Dr. FREDRICKSON. There are two principal reasons why we believe the construction of what is called an ambulatory care research facility, which will be joined to the present Clinical Center, is of extraordinary importance to the maintenance of the quality of the research program at NIH.

The first of these is the fact that we have now reached the limit of our capacity for outpatient programs. We have seen the number of such people coming to the Clinical Center double since 1971. We foresee the possibility that by 1980 there will be at least a further doubling, or could be, had we more facilities.

The nature of research is changing throughout the world, throughout the biomedical world. It is moving more toward the study of larger population groups and the study of people who are living in their own settings and not retained as inpatients.

The opportunity to discover more about modes of preventing disease, and to assess the effectiveness of some of the interventions and develop-

ments made possible by biomedical research, requires that we be able to study many patients but for short periods. They can come in and leave during the same day.

Therefore, the nature of research is clearly changing, and we require facilities to accommodate to that changing mode.

Mr. NATCHER. Your justifications indicate that a portion of the request for this facility is actually to modernize outmoded surgical, pathological, and radiological departments at the main building.

Dr. FREDRICKSON. That is correct. That is really the second reason why we need this facility; that is, to modernize our current facilities.

The Clinical Center is now almost 25 years old. It was designed back in the late 1940's. It was certainly one of the most modern of all hospitals in the world at that time but clearly the march of technology has outmoded it.

The present facilities for general surgery and for eye surgery, those used primarily by the National Cancer and the National Eye Institutes, is so severely outmoded, in regard to the size of both the operating rooms and the intensive care units, that I despair of our ability to continue surgery under these conditions, unless we take steps for renovation.

The radiology department is, like most radiology departments in the country, acquiring massive new technology in regard to scanning devices, ultrasound, which is still to come, computerized X–ray, which is already present to such an extent that we even have to use a large share of the existing waiting room space to accommodate some of this equipment.

While there will be a retirement of a few modes of radiation diagnostic techniques, it is clear that more space will be needed or we shall not be able even to maintain parity in this particularly important field.

Mr. NATCHER. Doctor, how much of the $21.7 million do you intend to use for this purpose?

Dr. FREDICKSON. None of the current $21.7 million first-phase funds will be used for reconstruction and renovation. An amount in the order of about $8 million will be included in the final total sum for the construction.

We will delay renovation until we have acquired the new space. In fact, we have no other way of doing it, and must wait until the final phase of the construction of the research facility.

Mr. NATCHER. Doctor Fredrickson, the committee is somewhat at a disadvantage in trying to place this current request in perspective since allocations for this account are so erratic. Can you tell us in general terms what the committee can expect in terms of a request for 1978 if this current $24.5 million request were approved? What could we expect in 1978, Doctor?

Dr. FREDICKSON. Then I think, Mr. Natcher, the committee could expect a request for $65.5 million in fiscal year 1978 which would be the balance of the sum required for the construction of the ambulatory care research facility. In fiscal year 1979 we would propose submitting a request for $7.7 million which would be for the renovation to the existing building 10, or Clinical Center, that now stands.

POTABLE WATER SYSTEM

Mr. NATCHER. You propose to put $200,000 into installation of a potable water system. What kind of system are you talking about now? Is this a new concept?

Mr. HOLLIDAY. The potable water system, as referred to in the report, consists of a project which we are planning in two stages: The first stage of the project in this fiscal year of 1977, and then the second stage in 1978. We propose to do the work in two steps to alleviate disruption to program activities.

The purpose of the project is to isolate laboratory water services from drinking water services provided to the patient care areas and cafeterias and other such areas of the building to obviate the possibility of cross-contamination. In addition, it is necessary to increase the water pressure on the upper floors of the building.

Mr. NATCHER. This is a new concept; right?

Mr. HOLLIDAY. Yes; this will be an improvement in the water distribution system.

Mr. NATCHER. Is there anything else you would like to add?

Mr. HOLLIDAY. No; thank you.

EXECUTIVE SALARIES

Mr. NATCHER. Under the "Office of the Director, salaries and expenses," we want to turn now to the Office of the Director account. This committee continues to be concerned with the issue of executive pay and its impact on staffing at NIH. We have just read about Dr. Rauscher's potential departure, and we are disturbed by rumors of other resignations.

Doctor, as you heard me say the other day, when Dr. Cooper was before the committee, you have around you a lot of awfully good people, recognized all over the United States. You have had them in this room every day since we started our hearings on the National Institutes.

How serious is this problem, Doctor?

Dr. FREDRICKSON. This is a continuing, and I think, increasingly serious problem, Mr. Natcher. The ceiling on civil service salaries that has been extant now for nearly 5 years, with the exception of the modest cost-of-living increase in ceiling last year, has left us in an extremely poor competitive position, a position which has long been an unfair one with regard to the private sector, primarily with the academic centers with which the NIH mainly competes for its expertise.

Selective increases permitted within the Federal sector have also aggravated this situation during the last several years.

We have great difficulty in retaining the high quality people that we need. I am very grateful for your comment, and agree with you, about the quality of the people that we have. Indeed, I pray that we can continue to hold them. But competition increases and we are at an increasing disadvantage in this regard.

Mr. NATCHER. Dr. Frederickson, we know on this committee that our new Secretary of Health, Education, and Welfare has only been with us a little over 6 months.

Dr. FREDRICKSON. That is correct, sir.

Mr. NATCHER. Have you had an opportunity to discuss this matter with him?

Dr. FREDRICKSON. We have had one opportunity to discuss it with him. Secretary Mathews has come out to visit the NIH, and it was among the many things we discussed with him. We have had an opportunity to, at least, acquaint him with the nature of the problem. He, being a university professor, realizes the competitive gradients that do exist, and we hope to have another opportunity to press forward on this problem.

Mr. NATCHER. You might in discussing it with him, Dr. Fredrickson, inform him that we are concerned on this subcommittee about this matter. I think I can make this statement for my friends on both sides. We are concerned about it. You might inform him that we are, Doctor, because it is a serious matter, and one that I think can be corrected and should be corrected.

Dr. FREDRICKSON. Thank you, Mr. Natcher, I will do so.

STANDARD LEVEL USER CHARGES

Mr. NATCHER. Now, you have changed the manner in which you show standard level user charges for NIH as a whole, but you show an increase of almost 30 percent for the Office of Director.

What about this?

Mr. SCHWARTZ. We have changed the way we account for our standard level user charge since we feel it is a more consistent and appropriate use of our account structure.

Last year we showed the entire amount for standard level user charges in the Office of the Director appropriation, even though the rental arrangements were of use to every appropriation at NIH.

We have now made a distribution of this charge to all of the Institutes based upon the percentage of budgeted positions that each appropriation has to the total. So therefore what we have is a fair share being allocated to all appropriations including the Office of the Director account.

MANAGEMENT FUND

Mr. NATCHER. Can you explain each Institute's assessment, how you determine each Institute's assessment from the standpoint of the management fund? How do you determine that, Mr. Schwartz?

Mr. SCHWARTZ. Yes, sir, that is correct. We have a methodology of distributing the management fund based upon the various activities in the management fund. An example of this would be the Clinical Center. The Clinical Center costs are allocated to each Institute based upon the number of beds assigned to that Institute as a percent of the total beds. Other activities such as Division of Research Services are distributed on the basis of number of intramural personnel. So we go through a calculation with a standard set of allocations both as to cost and as to application to Institutes.

FREEDOM OF INFORMATION AND PRIVACY ACTS

Mr. NATCHER. I believe the major responsibility for implementation of both the Freedom of Information Act and the Privacy Act fall in your office; that is correct, isn't it?

Mr. SCWARTZ. That is correct, in the Office of Director account.

Mr. NATCHER. What problems have you experienced now? Have there been unusual costs associated with this project?

Mr. SCHWARTZ. Both the Freedom of Information Act and the Privacy Act have created additional costs for us. There is no question about that. They are two complicated acts, and we are implementing them in the best possible manner that we can.

It has been expensive in terms of manpower and also costs applied. There is one special problem that we have associated with both laws, and that is in implementation of a research program.

I think Dr. Fredrickson might like to comment on how both acts provide problems in review of research awards.

Dr. FREDERICKSON. That is true, Mr. Natcher. There is one particular problem, for example, in regard to the material that is submitted for review of research fellowships. That information is now available to the applicant, under the Freedom of Information Act, and I think that it has caused a number of the individuals to blunt the candor of their comments. We fear that this may decrease our ability to make intelligent choices in that program.

SMALL BUSINESS PROGRAM

Mr. NATCHER. Mr. Schwartz, could you tell the committee what efforts you are undertaking to encourage small businesses by awarding them NIH contracts?

Mr. SCHWARTZ. We have a very active small business program. We have a Division of Contracts and Grants, with one staff member in that division with responsibility for implementation of this program.

We set a goal for NIH and monitor ourselves against that goal. This individual reviews all potential procurements that come through NIH for possibilities of utilizing small businesses. We work very closely with the Small Business Administration, I would also like to comment on our 8(a) setaside program. This is a program within Small Business where we have awards specifically designated for minority firms. We take these programs seriously, and we think we are doing a good job.

BIOMEDICAL RESEARCH ANALYSIS

Mr. NATCHER. Your justifications indicate that you will be completing a comprehensive analysis of programs and resources for biomedical research in the United States. What type of analysis are you talking about, Mr. Schwartz?

Mr. SCHWARTZ. NIH currently has underway the development of a second draft of an analysis of support of biomedical research and development by the different sectors of the national economy. This study which is tentatively entitled "National Support of Health R. & D." is being produced by the Office of Program Planning and Evaluation. It will provide a description and analysis of support, in the form of dollar obligations by the following: Federal Government, State government, industry, and nonprofit organizations (voluntary health agencies, private foundations, and institutions of higher education). It will provide information about each of these sectors as

sources of dollar support as well as performers of the biomedical research. The analysis will be most detailed for the Federal sector.

We also would like you to be aware that the Division of Resources Analysis within the Office of Program Planning and Evaluation has the responsibility of conducting a continued monitoring of these different sectors in terms of support for biomedical research and development, and has conducted a number of specialized studies on different aspects of this area.

Mr. NATCHER. When do you expect to complete this analysis?

Mr. SCHWARTZ. We expect to have it printed by the end of June.

Mr. NATCHER. The committee would like to have a copy of this report when you complete it.

Mr. SCHWARTZ. Yes, sir.

EVALUATION ACTIVITIES

Mr. NATCHER. With respect to your evaluation activities, what portion of this work is done directly and what portion is through contracts?

Mr. SCHWARTZ. We have a very small staff whose primary responsibility is evaluation, but a large proportion of the professional staff contributes some time to evaluation planning and the conduct of studies. Excluding the peer review system, which is itself an evaluative function, we estimate that about half of the NIH evaluation activity is performed directly by NIH staff and about half by contract using the 1 percent set-aside funds. One reason for the large proportion of in-house evaluation activity is that administration and organization problems of research support and the social and economic structures of the affected constituency are unfamiliar to many contracting firms. As the number of contractors able to deal with the complexities and idiosyncrasies of research programs increases, larger proportions of our evaluation activities will be performed through the contract mechanism.

Mr. NATCHER. What is the approximate budget in fiscal year 1976 and 1977?

Mr. SCHWARTZ. For fiscal year 1976, it is approximately $4.4 million for studies directed by NIH staff. The Assistant Secretary for Health and the Assistant Secretary for Planning and Evaluation in the Office of the Secretary will use another $4.6 million of NIH funds. In fiscal year 1977, we expect to spend another $5 million on our own studies and expect proportionate increases in the draw from ASH and ASPE.

Mr. NATCHER. Mr. Michel?

RESEARCH SAFETY STANDARDS

Mr. MICHEL. Dr. Stetten, I understand you are the chairman of the Advisory Committee established to establish safety standards governing research in the field of genetic manipulation. According to an article in the scientific journal "Science," that committee has developed a set of safety standards which many experts in the field consider as considerably weaker than those agreed upon by the international conference held at Asilomar to discuss how the new technique should be controlled. Do you agree and, if so, why?

Dr. STETTEN. I was appointed by Dr. Robert Stone, then Director, NIH, to serve as chairman of the Recombinant DNA Molecule Program Advisory Committee. In this capacity, I attended the Asilomar Conference and have chaired four meetings of this committee since that time. In addition, the members of this committee have been in frequent contact with each other and with other workers in the field by mail, telephone, and actual meeting. By the time of our third meeting, in July 1975, the committee had come to a set of guidelines which were assembled and given some distribution. There were a substantial number of letters which I received after limited distribution of these initial draft guidelines. The early letters were mostly, as indicated in your question, critical of our guidelines as being less constraining than was appropriate.

However, the later letters quite consistently adopted the opposite posture and criticized our guidelines for being too constraining and too severe, thereby impeding unnecessarily the progress of science. All of these letters were distributed to all members of the committee which met again in December with the intention of reviewing the guidelines. This action was satisfactorily concluded at La Jolla, December 4 and 5, and a set of guidelines was developed which was acceptable to all members of the committee, even though it represented in detail no individual member's complete viewpoint. Wherever doubts were expressed, the more constraining option was selected.

These guidelines have now been presented to the Director, NIH, who assembled an expanded Director's Advisory Committee which met for 2 days in open session. The contents of the guidelines were reviewed in considerable detail, and viewpoints from the members of the committee and from the interested public have been assembled. These viewpoints are now being critically studied in the Office of the Director, and it is my hope that within the next few weeks an accepted set of guidelines will be published. It is my expectation that in most regards the published guidelines will indeed resemble those put together at La Jolla in December.

Mr. MICHEL. Is it true that without strong safety standards, there is a possibility that some of the so-called "recombinant DNA molecules" could escape from the lab and could cause new and uncontrollable epidemics?

Dr. STETTEN. The answer to this question at this time is "Yes." The technology of recombinant DNA molecules is a young technology and only beginning to be explored. The assignment of our committee on recombinant DNA molecules has been to attempt assessment of the likelihood of this and other adverse consequences from such research. If the benefits anticipated seem very great and the hazards seem modest and controllable, then the inclination is to proceed. The purpose of our guidelines is, first, to define experiments, the hazards of which are so great that they are not to be performed under any circumstances, and, second, to consider other types of experiments which may be performed and to define the containments which are appropriate for each type of experiment. The general principle accepted has been that the greater the risk of adverse consequence, the more rigorous is the required containment.

Two forms of containment have been defined: (1) physical containment, which means the interposition of a physical barrier between the laboratory operation and the outside world, and (2) the biological containment, which means the choice and manufacture of living organisms which have been "disarmed" so that they cannot survive in the event of a spill. Considerable progress has been made in both of these directions, and it is the uniform judgment of our committee that for each type of experiment which has been considered, entirely reasonable and conservative constraints are imposed upon the conduct of the experiment. By virtue of these considerations, it is our expectation that scientific progress will be permitted to continue and at the same time the investigator, his associates, his community, and his environment will be protected.

SALARIES

Mr. MICHEL. According to an article in the Star the other day, the Director of NIH receives a base salary of $37,800, but bonuses and allowances increase it to $52,700. What is the nature of these bonuses and allowances?

Mr. SCHWARTZ. Dr. Fredrickson is a commissioned officer in the U.S. Public Health Service with the rank of Assistant Surgeon General (pay grade 0–8). As such, he receives the same pay and allowances as a two-star general or admiral, viz:

Base pay	$37,800.00
Special incentive pay [1]	4,200.00
Quarters allowance	3,830.40
Subsistance	636.60
Continuation pay [1]	6,000.00
Total	52,467.00

[1] Applicable only to officers who are physicians.

Mr. MICHEL. How many other officials in NIH actually receive a higher than base salary through bonuses and allowances?

Mr. SCHWARTZ. 239 other commissioned officers receive a gross income (base pay plus bonuses and allowances) in excess of $37,800. Most of these gross incomes range from $38,800 to $50,000.

Physicians, pay grades 0–7, 0–6, 0–5	209
Dentists, pay grades 0–6, 0–5	29
Veterinarians, pay grade 0–7	1

Mr. MICHEL. The Director of the Cancer Institute apparently is contemplating quitting because his $37,800 salary is too low. Is there widespread discontent at NIH over the salary levels?

Mr. SCHWARTZ. Salary levels are causing significant problems in getting and keeping qualified people for key managerial positions as critical clinical specialities.

DISSEMINATION OF RESEARCH RESULTS

Mr. MICHEL. Have you as yet begun the increased dissemination efforts called for by Congress, or are you still just awaiting a study report?

Mr. SCHWARTZ. We have begun several of the activities which were listed in the "NIH Plan of Action for Improving the Dissemination of Research Results" submitted to the Congress in April 1975. These

steps include arrangements for expanding the services available through our cancer communications network in Wisconsin to include professional telephonic consultation on a wide range of diseases, preparation of material for publication of monthly research reviews in the Journal of the American Medical Association, beginning of program production for relay by the Communications Technology Satellite. A detailed report of progress on the items in the "Plan" was filed with the Senate Appropriations Committee, January 28, 1976. I will provide you with a copy of the report.

Mr. MICHEL. What are the "increased responsibility and workload" which you are contemplating for the Director's Office as part of the effort to increase dissemination?

Mr. SCHWARTZ. We have set up a "task force on communications" of senior scientists and administrators from several of the Institutes which is advisory to the Director in our program to improve information dissemination. The staff support for the task force is provided by the Office of Communications of the NIH Director's Office. At this time two upper level information professionals are assigned full time to the Task Force, and we plan to make use of outside consultants as the growing program requires.

[The report referred to follows:]

REPORT ON IMPLEMENTATION OF NIH PLAN OF ACTION TO IMPROVE DISSEMINATION OF RESEARCH RESULTS, JANUARY 28, 1976

At the instruction of the Senate Committee on Appropriations the NIH in April 1975 submitted to the committee a plan of action for improving the dissemination of the information derived from biomedical research.

Listed below are the eight specific elements of the plan and under each is a description of the corresponding action by NIH.

1. "That a central unit within the Office of the Director, NIH, be responsible for stimulating, coordination and evaluating the Agency's efforts in dissemination of research results. In performing its function the unit should seek and use the advice of non-Federal health professionals, communications experts and scientists."

The Office of Communications, a component of the Office of the Director, NIH, has been designated as the unit responsible for stimulating, coordinating and evaluating NIH efforts in disseminating research results.

Policy guidance and advice for the Director in carrying out the dissemination function is provided by a task force on communications which was established in September 1975. A senior information officer has been assigned full time to coordinate staff support for the task force. Members of the task force are:

Dr. Robert M. Bird—Director, Lister Hill National Center for Biomedical Communications, National Library of Medicine.

Dr. Philip S. Chen, Jr.—Assistant Director for Intramural Affairs, NIH.

Dr. Ronald G. Crystal—Chief, Pulmonary Branch, National Heart & Lung Institute.

Dr. Diane J. Fink—Director, Division of Cancer Control and Rehabilitation, NCI.

Dr. Phillip Gorden—Acting Clinical Director, National Institute of Arthritis, Metabolism, and Digestive Diseases.

Dr. Brigid G. Leventhal—Head, Chemoimmunotherapy Section, Pediatric Oncology Branch, NCI.

Dr. David P. Rall—Director, National Institute of Environmental Health Sciences.

Dr. Solomon Schneyer—Director, Division of Program Analysis, Office of Program Planning and Evaluation, NIH.

Dr. David B. Scott[1]—Director, National Institute of Dental Research.

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[1] Appointed in January 1976.

Dr. John R. Seal—Acting Deputy Director, National Institute of Allergy and Infectious Disease.

Dr. Jim L. Shields—Assistant Director for Health Information Programs, Office of Prevention, Control and Education, National Heart & Lung Institute.

Mr. Storm Whaley—Associate Director for Communications, NIH, Chairman.

On December 3, 1975, a subcommittee of the task force was set up to identify and recommend topics for communications emphasis. The list of subjects is subject to constant review and is based on the "clinical significance" of the topics (is the problem widespread? is new information regarding it available? et cetera).

The "emphasis list" will be used as a principal source of subjects for communication by the various means described in the plan. The list is not intended to limit the range of subjects communicated but will provide an important tool for coordination of dissemination efforts directed to the general public, practicing health professionals and scientists.

Currently, the subjects recommended for emphasis concern clinical problems in which recent advances can make a difference in diagnosis, management or treatment. Examples are "Evaluation and Management of High Blood Pressure," "Management of Asthma," "Combined Therapy for Breast Cancer," "The Use of Psychotropic Drugs for Mental Illness," "Dental Caries," "Drugs for Controlling Cardiac Arrhythmias," "Management of Diabetes," "Diagnosis and Management of Childhood Cancer," "Current Applications of New Technological Developments in Diagnosis—whole body scanner, electrocardiography, et cetera."

To date the task force has consulted informally with a variety of communications experts from the public media, scientific and professional journals as well as from the electronic media. A fund of $10,000 has been made available to the task force to pay the costs of travel and per diem of additional consultants including practicing health professionals and others who can provide insight on the problems addressed by the task force.

We do not plan to establish a formal external advisory committee for the dissemination program, but will make use of the NIH Director's Advisory Committee as the nucleus of a counterpart to the task force on communications.

Our "assessment of the receptivity of those in the health care community to the various modes of communication" has been based, up to this time, on existing data from various studies (for example, a 1974 study made by the Food and Drug Administration on the sources of biomedical information used by 20,000 practicing physicians, and a National Library of Medicine supported survey of Vermont-New Hampshire physicians recommendations for TV programing in continuing education).

In addition, we have begun discussions with representatives of the American Academy of Family Physicians (AAFP), a key group, regarding a survey of a sample of their membership. The AAFP Committee on Clinical Investigation maintains a panel of 1,500 to 2,000 physicians who have volunteered to participate in the type of assessment we need to make. We consider that the existence of this group provides a convenient and useful opportunity to poll an important segment of physician population on the value of some of the steps we have taken or plan to carry out. After some of the projects described in the report have been in operation long enough to achieve measurable results we will use the AAFP survey mechanism.

2. "Promote cooperative efforts with other Federal and non-Federal agencies in carrying out dissemination of research results."

Following are examples of NIH cooperative efforts in dissemination:

NIH public health education activities are coordinated with the Bureau of Health Education, a component of the PHS Center for Disease Control. In addition the research findings of NIH are used as the basis of informational activities by the other agencies of the Public Health Service.

The NIH is actively participating in the intradepartmental advisory committee on health education, which is advisory to the Bureau of Health Education. The Bureau is the focus of activities by the Department of Health, Education, and Welfare related to the health education of the public. A complementary, privately funded organization, the National Center for Health Education, was established in the fall of 1975. The National Center is designed to concentrate on leadership functions which no other agency can deliver to avoid duplication of other public and private resources.

The Communications Technology Satellite (see topic 5 below) will be used extensively by the Health Resources Administration, PHS. The facilities established by HRA funding for the CTS experiments will be available to NIH for

its research information dissemination activities, particularly in continuing education for health practitioners and for students in health professional schools.

The NIH is now supplying professional materials (prepared by NINCDS) in videotape form for the use of the professional staffs of a number of Veterans' Administration hospitals.

Informational materials on NIH research are being mailed regularly to all professional standards review organizations.

The individual institutes continue to have close relationships with their counterpart voluntary health organizations and professional societies.

Much of the research material supplied in the highly effective science writers briefings conducted each year by the American Cancer Society and the American Heart Association comes directly from the NIH.

The NIH cooperated with the National Technical Information Service of the Department of Commerce in a national conference held at NIH November 6–7, 1975, on medically related technical developments. Some 200 representatives of private industrial firms attended the meeting to learn of federally discovered, medically related processes, products or devices which lend themselves to development for production.

The national high blood pressure education program is a current example of cooperative efforts involving Federal and non-Federal agencies in a public health education program. The list of active participants in the program includes the Veterans' Administration, the Health Services Administration, the Health Resources Administration, the Food and Drug Administration, the Department of Transportation, the Department of Defense, the Environmental Protection Agency and the Department of Agriculture. Non-Federal cooperators include the American Medical Association, the National Medical Association, the American Osteopathic Association, the American Dental Association, the American Hospital Association, the American Heart Association, the American Academy of Family Physicians, the American College of Cardiology and the American College of Physicians.

The NIH is engaged directly in dissemination of research findings to the public, to the professions, and to the research community, and will continue to do so. It occupies a unique role vis-a-vis the research community since it carries out and funds a large and integral part of the total national biomedical research effort. Communications within science through the use of proven and established means will obviously continue to be a prime responsibility of the NIH and the National Library of Medicine.

While there are many existing channels for communications between the scientist and the practicing health professional, the NIH recognizes a special responsibility to make certain that significant research findings are, in fact, communicated expeditiously. Many of our current and planned efforts are directed to this end.

Other Federal agencies, particularly the CDC's Bureau of Health Education, are engaging with the problem of health education of the public. We believe the NIH should continue, and intensify public health education within a coordinated effort, shared with other Federal agencies.

3. "Initiate pilot studies to test feasibility of establishing regional information centers to promote comprehensive telephonic consultation service for practicing health professionals, based on existing academic health centers and networks of NIH-supported categorical disease centers."

An exploratory study has been initiated at the University of Wisconsin in Madison under which the cancer line service established there last year will be expanded to include consultation service for Wisconsin physicians and other health professionals covering the full range of disease categories. The Department of Continuing Education of the University of Wisconsin School of Medicine, is arranging for appropriate clinical faculty members at the school to respond to incoming calls.

It is worth noting that the University of Alabama Medical Center has successfully operated a similar service for more than 6 years. The Alabama "Medical Information Service by Telephone" (MIST) was established under the Regional Medical Program Service. Because of its perceived value it is now supported by State funds.

The Wisconsin study will be subject to continuous evaluation to determine if it is useful to health professionals, if it is cost effective, and if it lends itself to adaptation to other regions.

As a "back up" to the Wisconsin experiment a direct telephone link will be set up between Madison and Bethesda for systematic consultation on problems concerning which the Wisconsin center feels the need for further information. The same service will be made available to the Alabama "MIST" and other similar operations.

4. ". . . that NIH prepare and publish in media widely used by physicians and other health professionals a brief monthly review of advances in medical knowledge selected on the basis of their current clinical significance."

Arrangements have been made for the preparation of the monthly research reviews and publication of the first review in the Journal of the American Medical Association (JAMA) is tentatively scheduled for April 1976.

This activity is considered of key importance because the material selected and developed for it will be used as the source for many forms of communication other than journal publication.

Topics for the monthly review will be identified and recommended by the task force and the JAMA articles will be prepared by writers experienced in communication with health professionals.

Our purpose will be to select from the wide range of research findings and to communicate effectively a limited number of significant developments which deserve priority attention.

5. ". . . that NIH take all necessary steps to utilize fully new communications technology including the Communications Technology Satellite."

The National Library of Medicine through its Lister Hill National Center for Biomedical Communications is actively engaged in the development of new means, and improvement of existing methods, for communication of biomedical information.

During the past year the center has focused its attention on advanced planning for the use of the Communications Technology Satellite (CTS—a joint United States-Canadian project). It has committed more than $2 million for development of facilities to be used in the experiments the satellite will make possible for the health agencies.

The CTS will permit, for the first time, an assessment of the potential of nationwide two-way transmission of scientific data, face-to-face conferences among scientists via color television, the transmission of training films and videotapes to remote locations, and a variety of other uses for the benefit of scientists in many fields. Up to 6 hours per week have been set aside for educational, service, and research use in the health field.

The Health Resources Administration has already committed approximately $2 million for health experiments. Initial projects will include the use of the CTS as a link from Bethesda to at least six sites, including the Seattle, Wash., area.

The CTS was launched successfully January 17, 1976, and upon completion of the facilities test period, is expected to be available for communications experiments in the fall of 1976.

In addition to the above experiments, the NIH is exploring the possibility of using the satellite for transmission from Bethesda of research information programs for health professionals. We will look into the potential use of the CTS as a means for feeding programs to closed-circuit television networks now connecting hospitals and clinics in a number of areas in the Nation.

Recognizing that the value of any such system for communicating research-derived information to health professionals is determined by the effectiveness and quality of the individual program presentation, the research institutes have elected to experiment with program production prior to funding the necessary additional installations which would permit direct relay from Bethesda to selected receiving points in various parts of the country.

Accordingly, an initial fund of $100,000 has been set aside for the production of a few test programs on clinical subjects. Arrangements have been made to provide these programs by tape and film to operating networks in New Hampshire, Vermont, Indiana, Louisiana, Washington State, and other areas. From the experience gained in these tests it is believed that more effective programmatic use can be made of the CTS opportunity. Topics for the programs will be selected with the advice of the Task Force on Communications.

An example of advantageous use of television for dissemination of scientific information is a seminar, conducted in November 1975, which linked audiences in 24 cities in the United States and Canada.

This privately funded seminar on oral contraceptives was moderated by Dr. Ronald A. Chez, National Institute of Child Health and Human Development and brought together an estimated 10,000 physicians in the cities on the network. Provision was made for questioning of the panelists by physicians at the receiving points. The network used conventional microwave relay and coaxial cable at a cost of more than $300,000 for the 3-hour period. If the satellite broadband network system had been operational, the cost of transmission would have been greatly reduced.

The technical experiments to be conducted on the CTS by the Lister Hill Center will further the advance of a highly promising means of communication. For it to be effective in the dissemination of research information, however, serious attention must also be given to the form and substance of the information transmitted. We have taken an important first step to serve his purpose.

6. "* * * The NIH increase support to the National Library of Medicine to expand the National Biomedical Communications network it is developing."

The CTS experiment described in item 5 above is a principal component of the NLM's current activity in developing a biomedical communications network. In looking to the future, experience gained at this time through the use of the satellite and other new communications technologies may prove to be highly important for continued improvement in the dissemination of research information.

The increase requested for the support of the NLM in the President's 1977 budget is a reflection of general concern for improvement of information dissemination.

7. "* * * that the NIH increase the output of health education information by the mass media, especially audiovisual and videotape material for dissemination through radio and television including cable TV and closed circuit television."

At the time the NIH action plan for improving the dissemination of research information was submitted, the various institutes had held a few state-of-the-art briefings on research progress for science writers representing the Nation's largest newspapers, magazines, and the electronic media. Because of the apparent success of such efforts it was recommended in the plan that at least six such briefings be scheduled annually. Five briefings have been held since April 1975.

Full presentations were made on:

Cell biology.
General progress in eye research.
Fertility and the working woman.
Hypertension.
Immunology.

Additional briefings will be held during 1976 on:

Virus research.
Environmental factors in health.
Cell surface receptors.

The briefings are an effective means for assisting reporters and science writers in generating authoritative reports for the general public on current research progress, and has resulted in a large number of nationally distributed articles. More important than the immediate news which may be reported from the briefings is the increased store of knowledge they make available to the reporters. Subsequent stories involving the subjects covered in the briefings can be based on more comprehensive, accurate and current information. This in turn is providing the public with a new depth of understanding of the purposes and products of biomedical research.

The NIH has also cooperated fully with and provided authoritative input for the annual scientific briefings held by voluntary organizations like the American Heart Association and the American Cancer Society.

The 1975 plan of action included several recommendations for changes in the content and quantity of public service announcements being made available to radio and television stations. These changes have been made.

Mailings of public service radio messages are now going to each of the approximately 6,000 commercial AM and FM stations of the country. (In April 1975 the messages were going to approximately 2,000.)

The format of the messages has been improved to increase their impact, and each is designed to provide a substantive health message. Formerly our announcements concentrated on information about available leaflets, et cetera.

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In addition two 30-second color film public service messages have been supplied to each commercial VHF and UHF television outlet in the United States. Three more are scheduled for production and distribution this year.

This increased activity was recommended in the plan submitted to the Senate.

The Audiovisual Branch of the Office of Communications has begun regular informal surveys by telephone to ascertain acceptance and usage of our materials by television stations. Random sampling indicates that about 66 percent of the stations carry the NIH messages. Our radio materials are accompanied by user-reply cards which indicate a high level of acceptance and use.

A new staff member having recent experience in television and the public relations field has been added to the Audiovisual Branch. His function is to improve and maintain liaison with the broadcast media.

A special effort has been made during the past year to establish close liaison with nationally circulated women's magazines. Since April 1975, the News Branch of the NIH Office of Communications has provided 8 full length and 50 brief research features (all of which later appeared) to Harpers Bazaar, Vogue, Lady's Circle, Good Housekeeping, Ladies Home Journal, and Women's Day. Some of the topics were suggested by the magazines, others by the News Branch.

The NIH has six exhibits in the HEW Bicentennial Exhibit Center, which opened January 19. The Center is located in the new South Portal Building near the Capitol on the Mall. It is estimated that at least 1 million of the 25 million persons expected to visit the Mall during 1976 will see the NIH displays.

Two new NIH public information activities are directed to the school-age audiences. The first such activity involves a national periodical for high school students.

Arrangements have been made for NIH to supply "Current Health" magazine with biomedical information on a regular basis. "Current Health" is a monthly publication for high school students and has a circulation of 1 million. Material for articles on digestive diseases, sudden infant death, polio, and other problems has been provided to the magazine during the current academic year.

A 15-minute instructional film, "Invaders and Defenders," has been prepared and will shortly be released for use in junior high schools across the Nation. The principal theme of the movie is research related to immunology. Accompanied by an illustrated users guide to enhance its utility in the classroom, the sound-and-color film is designed to supplement junior high school curriculum in health and science. The film, to be distributed through Association-Sterling Films, has already been ordered by 200 schools.

Although primarily concerned with public information activities the News Branch of the NIH Office of Communications has begun providing materials to various professionals publications for regular use.

In April 1975 we began supplying an in-depth continuing education series for Pharmacy Times, a monthly professional magazine distributed to 80,000 pharmacists.

An indication of the nature of this activity is best given by listing the topics of the articles published in Pharmacy Times:

April 1975—"Continuing Education: The Pharmacist's Role in Managing Hypertension."

May 1975—"Continuing Education: What You Should Know about Stroke."

June 1975—"Update on Diabetes: NIH Continuing Education Series."

July 1975—"Continuing Education from NIH: The Challenge of Pain."

August 1975—"Continuing Education: What You Should Know about Cancer."

September 1975—"What You Should Know About Acute Respiratory Disease."

October 1975—"Continuing Education: What You Should Know about Parkinson's Disease."

December 1975—"Continuing Education—Update: What You Should Know about the Epilepsies."

January 1976—"What You Should Know about Asthma."

February 1976—"What You Should Know about Myasthenia Gravis."

March 1976—"What You Should Know about Tuberculosis."

Some of the above articles have been reprinted in full in Resident and Staff Physician (100,000 circulation) and Medical Times (50,000 circulation).

Since April 1975 the NIH News Branch has distributed the biweekly series, "News and Features from NIH," to the more than 200 Professional Standards Review Organizations. The monthly Research Reviews to be prepared by NIH will be added to the PSRO mailings.

A current example of an important additional activity of the NIH Office of Communications is providing extensive material to the authors of "The Complete Health Book" now in preparation. The aim of the book is patient education and it will deal with current state of knowledge regarding the major disease entities and life processes. We have been asked by the authors for assistance in providing complete and accurate source material from all components of NIH and to list and characterize the materials and services available to the public through NIH.

Although the national high blood pressure education program predates the 1975 plan of action, the continuing program of this important public health education activity has begun to achieve the results for which it was established. Data released in December 1975 indicated that since the inception of the program in 1972 there have been (a) sharp increases in the initial and total patient visits to physicians for hypertension and hypertensive heart disease; (b) a sharp reduction in the number of people with unsuspected and undiagnosed hypertension; and (c) a marked increase in the number of hypertensive patients whose blood pressure is under adequate medical control.

Initial patient visits to physicians for hypertension and hypertensive heart disease have increased 38 percent since 1971, and total visits for these conditions have increased by 40 percent, at a time when the visits to physicians for all causes increased by 17 percent.

The national high blood pressure education program is coordinated by the National Heart and Lung Institute and involves participation of more than 150 national organizations and groups—Federal, private, and professional, several of which were listed under (2) above.

8. "* * * conduct a series of national workshops to review existing means of disseminating research information, identifying needed improvements and suggesting steps for implementation."

In May 1975, the National Library of Medicine conducted a national workshop with 12 medical educators, including medical school deans, directors of Continuing Medical Education, and others, to discuss the role of the Lister Hill Center in improving the continuing education of health professionals.

On December 10, 1975, a second national workshop was conducted by the National Library of Medicine with medical publishers, medical writers, a national network broadcaster, and a practicing physician to discuss ways to improve the transfer of biomedical information to physicians and the public.

Inasmuch as the continuing education of health professionals is a major object of the dissemination of research-derived information the above NLM activities in this area are considered to be of primary importance to NIH efforts for communications improvement.

Two important national meetings related to biomedical communications are planned for the coming year. A colloquium on "The Bicentennial of U.S. Medicine" will be hosted May 6–7, 1976, by the National Library of Medicine in cooperation with the Josiah Macy Jr. Foundation. Distinguished physicians, scientists, and educators will examine the progress of U.S. medicine and assess prospects for the future. Topics will include medical education, public health and preventive medicine, biomedical communications, and the Federal role in research.

A national bicentennial symposium jointly sponsored by the NIH and the District of Columbia Medical Society is tentatively scheduled for September 16–18, 1976. The topic for the symposium is dissemination of research information. The preliminary title of the meeting is "Bridging the Gap Between Research and Practice."

Every effort will be made to focus national attention on the symposium.

CONTRACTS AND GRANTS

Mr. MICHEL. In referring to contracts and grants, 24,000 are cited. Can you give us a general breakdown of these projects?

Mr. SCHWARTZ. The Division of Contracts and Grants is responsible for the business management of contracts and grants activity throughout the NIH. In this regard, the Division's mission is directed toward promoting continuing improvement in the quality and effectiveness of NIH contract and grant activities by providing policy leadership and guidance in the overview and servicing of approximately 24,000 grants and contracts. These projects may be generally classified as:

Grants:	*Estimated percentage*
Research projects	59
Program projects and center grants	5
Research career	5
Research training	9
Fellowships	9
Construction and others	3
Contracts: Negotiated contracts	10

Mr. MICHEL. What kind of an effort do you make to insure against fraud and abuse with respect to the grants and contracts?

Mr. SCHWARTZ. The major effort in this area comes from Government auditors reviewing the records and programs of our grantees and contractors. Within DHEW the audit agency located within the Office of the Comptroller has this responsibility. The Division of Contracts and Grants Financial Advisory Services Branch provides a formal effort to insure against abuse with respect to grant and contract costs in its audit resolution, cost advisory support to program, and its indirect cost negotiation functions. The Division is not involved in disclosures or resolution of fraud allegations.

Mr. MICHEL. Is your office the one which negotiates with the various institutions regarding overhead or indirect cost?

Mr. SCHWARTZ. Indirect cost rates for educational and other nonprofit organizations are negotiated by regional comptrollers' offices. The Division of Contracts and Grants negotiates indirect cost rates with profitmaking organizations.

AFFIRMATIVE ACTION PLAN

Mr. MICHEL. What is the nature of this affirmative action plan which is cited in your justification?

Mr. SCHWARTZ. The NIH affirmative action plan is the principal instrument for establishing new policies and procedures and/or revising existing ones, where appropriate, for the purpose of upgrading the employability of minorities and women at NIH. That is to say, it serves to establish innovative and imaginative ways for increasing the ability of certain groups to compete on an equal basis in the existing job market.

As it relates to Federal EEO statutes, the NIH affirmative action plan is not unique. It is a basic civil service requirement under part 713 of the Federal Personnel Manual, which finds its basis in Executive Order 11478, and Public Law 92–261.

However, we do feel that the current AAP is unique to the agency inasmuch as it represents the first time that NIH has established specific and comprehensive goals and timetables for increasing minority and women employment. In addition, the plan has built-in mechanisms for monitoring and evaluating progress at suborganizational levels (bureaus, institutes, and divisions) in order to determine the overall effectiveness of the NIH equal opportunity program. Moreover, the plan specifically designates those responsible officials and/or services that will be held fully accountable for implementing specific action items (with related target dates) as spelled out in the plan.

VOUCHER AND VENDOR PAYMENTS

Mr. MICHEL. Your justifications refer to voucher and vendor payments. What do these involve?

Mr. SCHWARTZ. These refer to the payments for employee travel and for goods and services procured in the conduct of NIH research operations. They include payments for supplies, materials, equipment, and services required in support of program activities. During fiscal year 1975, the number of transactions of this type totaled 343.000. The estimate for fiscal year 1976 is 358,000 and for fiscal year 1977 it is 360,000. The terms voucher and vendor payments do not cover payments to R. & D. contractors or grant recipients.

AMBULATORY CARE RESEARCH FACILITY

Mr. MICHEL. Regarding the new ambulatory care facility, what is the projected completion date?

Mr. SCHWARTZ. The current schedule projects completion of the over a period of 12 to 24 months, beginning in the fall of 1980.

Mr. MICHEL. Will the facility be used prior to the time it is totally completed?

Mr. SCHWARTZ. It is anticipated that the parking structures will be occupied about mid-1978 and occupancy of the building will occur over a period of 12–24 months, beginning in the fall of 1980.

Mr. MICHEL. How reliable is that $95 million cost figure? Does it take into account projected inflation increases?

Mr. SCHWARTZ. The $95 million estimate has been prepared based on plans which are about 30 percent complete—that is, schematic plans. A more detailed estimate will be prepared at the point plans are about 60 percent complete, however, we fully expect to develop the facility within the cost estimate which includes a very preliminary cost estimate of $7.7 million for renovation of the existing clinical center building. This renovation will occur upon completion of the ambulatory care research facility annex. Inflation costs have been included in the estimate.

Mr. MICHEL. Design funds were appropriated way back in fiscal year 1973, yet, the design is only 30 percent completed. Why is it taking so long?

Mr. SCHWARTZ. Some delay occurred in the apportionment of the planning funds which were provided by Treasury warrant in lieu of an approprition for this project in 1973. Development of the program of requirements was completed in July 1974. The architect/engineer joint venture was engaged in March 1975 for planning and design of the facility.

Mr. MICHEL. When will design be completed?

Mr. SHWARTZ. Design of the first phase of construction including site work, building substructure, and parking is scheduled to be complete by December 1976. The remaining facility design is to be completed about September 1977.

Mr. MICHEL. When will construction begin, and how long will the first stage take?

Mr. SCHWARTZ. The first phase of construction is expected to begin about January 1977 and be completed about June 1978.

Mr. MICHEL. How much of the $95 million would be devoted to renovation of the existing facility?

Mr. SCHWARTZ. The current $95 million estimate includes $7.7 million for renovation of the existing facility. However, this is a very preliminary estimate of renovation costs and more recent planning developments indicate the estimate may be too conservative. We expect to have a better fix on this in the near future.

Mr. MICHEL. Will the new facility be fully utilized from the start, or has a lot of extra space been provided for future increases in need?

Mr. SCHWARTZ. It is expected that the facility will be occupied as rapidly as the program can be expanded. Some existing functions in crowded and obsolete space in building 10 will be moved into the new annex.

POTABLE WATER SYSTEMS

Mr. MICHEL. Is there a current problem with respect to the drinking water system that requires the construction of two separate systems?

Mr. SCHWARTZ. The current city water piping distribution system serves both the laboratory needs as well as patient care areas and other potable water needs. Funds are being requested to separate the piping systems to obviate the possibility of cross-contamination of drinking water and also to increase the water pressure on the upper floors of the building.

Mr. NATCHER. Mr. Schwartz, we want to thank you and your associates, and Dr. Fredrickson, of course, for presenting to the committee the budget request for the Office of the Director of Buildings and Facilities. Thank you very much.

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] *$25,400,000,* to remain available until expended.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Amounts Available for Obligation

	1976 Estimate	1976/1977 Transitional Quarter	1977 Estimate
Appropriation	$54,000,000	$ 750,000	$25,400,000
Unobligated balance, start of year	14,677,205	59,546,000	14,756,000
Unobligated balance, end of year	-59,546,000	-14,756,000	-6,575,000
Total, obligations	9,131,205	45,540,000	33,581,000

Summary and Explanation of Changes

1976 Budget Authority	$54,000,000
1976/1977 Budget Authority	750,000
1977 Budget Authority	25,400,000
Net Change	$24,650,000

Increases:

A. Program

1. Ambulatory Care Facility	+$21,700,000
2. Repairs and improvements, plant	+1,000,000
3. Repairs and improvements, program	+2,000,000
4. Master utilities extension	+500,000
5. Potable water systems	+200,000
Total, increases	+25,400,000

Decreases:

A. Program

1. Repairs and improvements, plant	-250,000
2. Repairs and improvements, program	-500,000
Total, decreases	-750,000
Total, net changes	+24,650,000

Obligations by Activity

Page Ref.		1976 Appropriation	1976/1977 Estimate	1977 Estimate	Increase or Decrease
271	Research facilities...	$ 624,625	$44,280,000	$24,191,000	-$20,089,000
271	Service and administrative facilities..	8,506,580	1,260,000	9,390,000	+8,130,000
Total obligations.....		9,131,205	45,540,000	33,581,000	-11,959,000

Obligations by Object

	1976 Estimate	1976/1977 Estimate	1977 Estimate	Increase or Decrease
NATIONAL INSTITUTES OF HEALTH				
Other Services.....	$1,389,316	$ 223,000	$ 377,000	+$154,000
Lands and structures.....	7,692,280	24,277,000	28,124,000	+3,847,000
Subtotal.....	9,081,596	24,500,000	28,501,000	+4,001,000
ALLOCATION TO GENERAL SERVICES ADMINISTRATION				
Other services.....	49,609	40,000	80,000	+40,000
Lands and structures.....	---	21,000,000	5,000,000	-16,000,000
Subtotal.....	49,609	21,040,000	5,080,000	-15,960,000
Total obligations by object..	9,131,205	45,540,000	33,581,000	-11,959,000

Actual

Buildings and Facilities

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
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	93,000,000	41,000,000	54,000,000
1977	25,400,000			

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	1976 Revised President's Budget	1976 Appropriation	1976/1977 Estimate	1977 Estimate	Increase or Decrease
Research facilities.....	$ ---	$51,000,000	$ ---	$21,700,000	+$21,700,000
Service and administrative facilities.....	3,000,000	3,000,000	750,000	3,700,000	+2,950,000
Total.....	$ 3,000,000	$54,000,000	$750,000	$25,400,000	+$24,650,000

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.

Ambulatory Care Facility

1977 appropriation estimate..... $21,700,000

The Ambulatory Care Research Facility is proposed as a major addition to the Clinical Center to be constructed on a site adjacent to the north face of the existing building. The new facility will make possible increased emphasis on ambulatory patient versus in-bed patient type clinical research in an effort to address the need for expediting the translation of basic research results. The project will also include modernization of existing outmoded and inadequate clinical support departments such as surgery, pathology and diagnostic radiology.

In 1973, $3,580,000 was provided for the design of the facility and the design contract was awarded in March 1975. In 1977, $21,700,000 is requested to support the first phase of construction. The total project construction is estimated to cost approximately $95 million dollars.

Repairs and Improvements - Plant

1977 appropriation estimate..... $1,000,000

In 1977, $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 37 years.

Repairs and Improvements - Program

1977 appropriation estimate..... $2,000,000

In 1977, $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.

Master Utilities Extension

1977 appropriation estimate..... $ 500,000

In 1977, $500,000 is requested for the extension of communication and other miscellaneous utility systems.

Potable Water Systems

1977 appropriation estimate..... $ 200,000

In 1977, $200,000 is requested for the first phase of the project for the protection of the potable water systems in the Clinical Center. This project will provide two separate water systems, replacing a single system, to prevent cross-contamination between laboratories and patient care areas.

NATIONAL INSTITUTES OF HEALTH

Buildings and Facilities

Program Purpose and Accomplishments

Activities: Research Facilities and Service and Administrative Facilities

1976 Amount	1976/1977 Amount	1977 Authorization	1977 Budget Estimate
$54,000,000	$ 750,000	Indefinite	$25,400,000

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 1976:

Construction Completed

Master Utilities Extension (part)

Construction Contracts Awarded

Master Utilities Extension (part)
Improvements to Blue Collar Work Areas

Construction Contracts Continued

Electrical and Air Conditioning Improvements, Building 10
Medical - Pathological Incinerator

Design Contracts Continued or Completed

Ambulatory Care Facility
Environmental Health Sciences Center, North Carolina
Lister Hill National Center for Biomedical Communications
Master Utilities Extension (part)
Modifications to Waste Handling Facilities

Repairs and Improvements

Continuation of major repairs and improvements for both plant and program facilities.

Objectives in 1977

Construction Contracts Awarded

Ambulatory Care Facility

Construction Contracts Continued or Completed

Electrical and Air Conditioning Improvements, Building 10
Improvements to Blue Collar Work Areas
Master Utilities Extension (part)
Medical - Pathological Incinerator

Design Contracts Completed

Ambulatory Care Facility
Modification to Waste Handling Facilities

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

Office of the Director

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Amounts Available for Obligation 1/

	1976 Estimate	1977 Estimate
Appropriation	$17,896,000	$16,234,000
Proposed supplemental appropriation	474,000	---
Subtotal, appropriations	18,370,000	16,234,000
Comparative transfers to:		
"National Cancer Institute"	-943,000	---
"National Heart and Lung Institute"	-334,000	---
"National Institute of Dental Research"	-136,000	---
"National Institute of Arthritis, Metabolism and Digestive Diseases"	-285,000	---
"National Institute of Neurological and Communicative Disorders and Stroke"	-261,000	---
"National Institute of Allergy and Infectious Diseases"	-311,000	---
"National Institute of General Medical Sciences"	-76,000	---
"National Institute of Child Health and Human Development"	-169,000	---
"National Institute on Aging"	-100,000	---
"National Eye Institute"	-73,000	---
"National Institute of Environmental Health Sciences"	-120,000	---
"Division of Research Resources"	-35,000	---
"Fogarty International Center"	-23,000	---
"National Library of Medicine"	-179,000	---
(Transfer of Standard Level User Charges)		
Total obligations	15,325,000	16,234,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1976 - $14,100,000; 1977 - $14,100,000.

Summary of Changes

1976 Estimated Obligations	$15,325,000
1977 Estimated Obligations	16,234,000
Net change	+909,000

	1976 Base Pos.	1976 Base Amount	Change from Base Pos.	Change from Base Amount
Increases:				
A. Built-in:				
1. Annualization of 1976 pay increase	---	$474,000	---	+$168,000
2. Within-grade pay increases	---	177,000	---	+197,000
3. Increased postage rates	---	350,000	---	+105,000
4. Increased FTS rates	---	30,000	---	+6,000
5. Increased Bureau of Employment Compensation payments	---	20,000	---	+2,000
6. Increased per diem travel costs	---	129,000	---	+20,000
7. Increased Service and Supply costs	---	500,000	---	+70,000
8. Increased payment to NIH Management Fund	---	1,952,000	---	+301,000
9. Increased payment to NIH Management Fund for SLUC	---	265,000	---	+80,000
Total increases	---	---	---	+949,000
Decreases:				
A. Built-in:				
1. One less day of pay in 1977	---	11,407,000	---	-40,000
Total, net change	---	---	---	+909,000

Obligations by Activity

Page Ref.		1976 Appropriation Pos.	1976 Appropriation Amount	1977 Estimate Pos.	1977 Estimate Amount	Increase or Decrease Pos.	Increase or Decrease Amount
283	Program management	546	$15,060,000	546	$15,889,000	---	+$829,000
	Standard level user charge	---	265,000	---	345,000	---	+80,000
	Total obligations	546	15,325,000	546	16,234,000	---	+909,000

Obligations by Object

	1976 Estimate	1977 Estimate	Increase or Decrease
Total number of permanent positions.	546	546	---
Full-time equivalent of all other positions	46	46	---
Average number of all employees	565	565	---
Personnel compensation:			
Permanent positions	$9,715,000	$10,000,000	+285,000
Positions other than permanent	482,000	492,000	+10,000
Other personnel compensation	210,000	213,000	+3,000
Subtotal, personnel compensation	10,407,000	10,705,000	+298,000
Personnel benefits	1,011,000	1,040,000	+29,000
Travel and transportation of persons	129,000	149,000	+20,000
Transportation of things	6,000	6,000	---
Rent, communications and utilities	580,000	691,000	+111,000
Printing and reproduction	387,000	424,000	+37,000
Other services:			
Payment to NIH Management Fund	2,217,000	2,598,000	+381,000
Other	336,000	369,000	+33,000
Supplies and materials	142,000	142,000	---
Equipment	110,000	110,000	---
Total obligations by object	15,325,000	16,234,000	+909,000

Significant Items in House and Senate
Appropriations Committee Reports

Item	Action taken or to be taken
1976 Senate Report	
Dissemination of Research Results	
1. Before next year's hearings the Committee will expect a full report on the implementation of the NIH recommendations including an account of the cooperation it has had from other agencies and an assessment of the receptivity of those in the health care community to the various modes of the communication which have been discussed in the report (pages 34 and 35.)	1. The Director NIH appointed the "Task Force on Communication" on September 4, 1975. The establishment of this group was the first action step in the Plan and Report cited by the Senate. The Task Force is coordinating the further action steps recommended in the Report and will assist the Director in preparation of the "full report" called for in the 1976 Senate Report.

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	15,874,000	15,644,000	14,750,000	14,750,000
1976	16,941,000	16,567,000	14,851,000	
Supplemental	474,000			
1977	16,234,000			

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.

The figures presented in this table have been adjusted to reflect the transfer of major functions. This permits a more objective comparison of the amount contained in the budget year with amounts in prior years. For example, the responsibility for funding of standard level user charge payments to GSA is not the function of the Office of the Director in 1977. The amount originally contained in previous years for this particular program has been removed for comparability purposes.

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
1976	19,986,000	19,612,000	17,896,000	
Supplemental	474,000			
1977	16,234,000			

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

	1976 Appropriation		1977 Estimate		Increase or Decrease	
	Pos.	Amount	Pos.	Amount	Pos.	Amount
Program management	546	$15,325,000	546	$16,234,000	---	+$909,000

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 1977 budget contains only mandatory increases which are necessary to permit the Office of the Director to operate at the 1976 comparable level.

Program Plans for 1976 and 1977

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 education 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 approximately 24,000 active on-going projects.

The Office of the Director which provides overall program direction and central management services to the Bureaus, Institutes, and Divisions of the National Institutes of Health will in 1977 be required to handle the increased responsibilities and workload related to the following Congressionally mandated programs:

A. Dissemination of Research Information
B. The Freedom of Information Act
C. The Privacy Act
D. Protection from Research Risks

Summary of Requested Changes

Built-in items	Amount
1. Annualization of 1976 pay increase	+$168,000
2. Within-grade pay increases	+197,000
3. Increased postage rates	+105,000
4. Increased FTS costs	+6,000
5. Increased BEC payments	+2,000
6. Increased per diem travel costs	+20,000
7. Increased service and supply costs	+70,000
8. Increased payments to NIH Management Fund	+301,000
9. Increased payments to NIH Management Fund for SLUC	+80,000
10. One less day of pay in 1977	-40,000
Total.....	+909,000

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Program Purpose and Accomplishments

Activity: Program management

1976 Estimate			1977 Budget Estimate	
Pos.	Amount	Authorization	Pos.	Amount
546	$15,325,000	N/A	546	$16,234,000

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 division directors with the aid of staff specialists and operating personnel.

Accomplishments in 1976: In conjunction with its responsibilities of providing overall program direction and central management services the Office of the Director accomplished the following:

1. Developed and prepared the NIH Forward Plan and prepared the NIH Evaluation Plan.

2. Continued the evaluation function of NIH research contracting activities through Board of Awards and on site institute reviews to improve overall contract management.

3. Began implementation of the Freedom of Information and Privacy Acts.

4. Developed a concise, practicable and workable Affirmative Action Plan which initiates many reporting and evaluating points to better determine achievement and progress in eliminating problems related to discrimination practices.

5. Continued to develop and implement the Material Management System which will significantly improve voucher payments by capture and transfer of procurement and delivery data to support vendor payments with improved accuracy and speed.

6, Completed Modular Orientation Manual used for introducing new top level staff to NIH programs.

7. Completed an NIH-wide workload/manpower reporting system which will meet the position survey requirements of the DHEW Manpower Management Plan.

8. Revised the Upward Mobility College program to conform with GAO recommendations.

9. Designed work measurement standards for research contracting activities to enable B/I/D's to determine whether contracting offices are adequately staffed or whether a better balance or alignment of personnel is needed in the interests of achieving optimum efficiency.

Objectives for 1977: The Office of the Director in addition to handling the increased responsibilities and workload related to the dissemination of research results, the protection from research risks, implementation of the Freedom of Information and Privacy Acts, plans the following:

1. Revise the Institutional Guide to DHEW Policy and Regulations on Protection of Human Subjects.

2. Complete work on a comprehensive analysis of programs and resources for biomedical research in the United States.

3. Provide support for the external committee of scientists, health care providers and communications experts, and the internal committee of scientists and implement their recommendations for increasing and improving the dissemination of research results to the professional health care community and the public.

4. Improve and increase the efficiency and service to the public of NIH responses required under the Freedom of Information and Privacy Acts.

5. Implement a Civil Rights Plan to provide technical assistance to grantee and contractors to inform minorities' and women's institutions of NIH resources and to educate NIH employees of needs and concerns of minorities and women's institutions.

6. Actively pursue and continue the development of a viable Small Business Program at the NIH, including locating potential new small and minority business sources for contracting in the biomedical research area.

7. Work for the establishment of an inter-agency committee to discuss and develop consistent policy procedures for the resolution of significant findings in reports prepared by Federal Audit Agencies.

8. Improve the timeliness and usefulness of budget analyses by developing effective outlay forecasting and manpower justification techniques and by computerizing the basic budget information.

9. Provide continuing review and evaluation of B/I/D contracting and grants operations to develop the highest level of quality.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL INSTITUTES OF HEALTH

Office of the Director

Transition Quarter Analysis

	Budget Authority by Activity	
	1976 Estimate	Transition Quarter
1. Activity:		
Program management.....	$15,325,000	$4,259,000
Total.....	15,325,000	4,259,000

Explanation

The funds requested in the transition quarter will provide for 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 1976 modified by program impact and pay raise requirements.

Mr. NATCHER. We will also include in the record at this point a number of special reports prepared by the Department on NIH issues.

The committee will adjourn now until 10 o'clock in the morning.

[These reports follow:]

ACUTE RESPIRATORY DISEASE

When a recent report on civilian use of physician services appeared, it came as no surprise to the National Institute of Allergy and Infectious Diseases (NIAID) that 1 out of every 6 calls on a doctor's time is for the diagnosis and treatment of an acute respiratory infection. These infections, whether caused by viruses or bacteria, are seldom fatal but are extremely costly in terms of time lost from work and school.

In addition, in the case of viral respiratory diseases, an enormous amount of money is spent on medications which are not curative, but may make the patient "feel better."

In certain patients, viral infections of the upper respiratory tract can be extremely serious. This is particularly true in persons with chronic lung conditions, such as asthma, emphysema, and cystic fibrosis. Indeed, there is a well-founded suspicion on the part of some scientists that the development of chronic obstruction of the airway passages may be related to repeated attacks of acute respiratory disease.

The development of better means for preventing acute respiratory infections and for treating them is a goal of the NIAID. In pursuit of this goal, NIAID-supported scientists coordinate their research efforts with those of investigators sponsored by FDA's Bureau of Biologics, the Center for Disease Control, and the U. S. Army. Such coordination avoids overlap and duplication of efforts by Federal agencies.

Drug companies also carry out research on acute respiratory infections and, under certain conditions, an effective partnership can be arranged between private industry and the Federal government.

Obligations for programs in Acute Respiratory Disease

	1973	1974	1975	1976 Estimate	1977 Estimate
National Institutes of Health: National Institute of Allergy and Infectious Diseases	$6,691,000	$7,015,346	$7,001,857	$7,461,000	$8,351,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Influenza

One of the most puzzling of acute respiratory diseases is influenza. The disease has long been recognized and the causative virus was isolated some 40 years ago; but control of the infection, in populations or in the individual, has been elusive.

The answers to influenza, as with few other diseases, seem to lie in a definitive understanding of the causes and nature of the genetic changes which take place in the virus itself. During the last few years this understanding has begun to come from basic studies of influenza viruses.

Scientists know that the influenza virus occurs in three immunologically distinct types -- A, B, and C. Local outbreaks and epidemics are caused more frequently by type A than by B, while type C rarely causes detectable disease.

Investigators have concentrated, therefore, on the influenza A virus and few microorganisms have been more intensively studied. These studies have shown that each year the flu virus changes slightly and that every 10-12 years a major modification takes place, rendering whole populations susceptible to the new strain.

The shifty nature of the influenza virus is related to changes in two chemical substances found on the outer surface of the virus. When these substances -- hemagglutinin and neuraminidase -- were identified, during the 1960's, as the antigens most responsible for stimulating the body's immune response to influenza, it became possible to provide a rational explanation for some of the mystifying relationships long noted between human and nonhuman influenza viruses and between strains circulating today and in years past.

The last major shift in the influenza A virus -- and the last world-wide epidemic -- took place in 1968. This was the Hong Kong flu. The next such pandemic is predicted for the late 1970's. By then scientists hope to be in a position to blunt its impact as well as to acquire information still needed to control these periodic outbreaks.

The virus. Over the years scientists have explored the genetic makeup of more than 100 respiratory viruses. They have found that, in general, these agents consist of a continuous strand of nucleic acid (RNA or DNA) which are the genes that carry instructions for viral self-duplication.

But the influenza virus is different. Its nucleic acid -- RNA -- consists of 7 to 10 discrete pieces, each of which controls a specific viral function. The fragmented nature of this genetic material is believed to be the key to the influenza agent's unique and puzzling ability to undergo periodic changes in its hemagglutinin and neuraminidase. Indeed, in the laboratory, "recombination" or reassortment of genes during simultaneous infection of the same cell with different influenza A viruses yields new viruses that differ from both parents. This recombination has also been experimentally demonstrated in mammals and birds.

Information on how frequently such recombination occurs in nature and how important such a phenomenon may be in explaining the periodic appearance of "new" viruses is expected to be forthcoming from research supported by NIAID. A contract was awarded during the past year to Dr. Robert G. Webster of St. Jude Children's Research Hospital, Memphis, Tennessee, to set up a special laboratory which will serve as the focus for an international network of investigators checking on influenza infections in domestic and wild animals and birds.

Through study of viruses causing these infections, the Tennessee scientists hope to learn whether new pandemic viruses arise by the recombination of genes from human viruses and genes from animal or bird strains. Of special interest to Dr. Webster's group will be animal and avian viruses from the Orient where past experience has shown a particular likelihood for the emergence of new flu virus strains.

The Memphis laboratory will also work with the World Health Organization and will serve as a central "antigen bank", retaining all identified virus samples in anticipation of a new pandemic.

Epidemiology. Other approaches to the epidemiology of influenza are being pursued at Baylor College of Medicine, Houston, where, last year, NIAID established an Influenza Research Center. At the Center Dr. Robert Couch and his associates have already initiated a variety of surveillance studies designed to detect the earliest signals of influenza activity in a community.

For example, they have set up a system for receiving blood samples from all patients undergoing tests at a number of community hospitals and laboratories. Antibodies (protective substances) in the sera will be identified by the scientists so they will know, in advance of a possible winter outbreak of respiratory disease, what degree of protection individuals in the community have against a specific influenza strain. This kind of information is considered essential for accurate prediction of the occurrence and impact of an influenza epidemic.

The experience of family groups with influenza virus is also being studied by Dr. Couch and his co-workers. Present knowledge of the natural history of influenza comes from studies of persons at a single time period and of some communities over long periods of time. Unfortunately, in the community studies, population shifts have invariably occurred about every 18-24 months as persons have moved in and out of an area. Consequently, there is considerable uncertainty regarding such questions as the duration of immunity to influenza infection and the frequency and consequences of reinfection.

By studying a single group of 100 families over a period of about 5 years, the Baylor scientists expect to clear up a number of these questions. Weekly telephone contacts will be maintained by the Baylor staff and parents are being asked to contact the Center if any respiratory illness occurs in a family member. In such an event, all members of the family will be examined and specimens obtained for virus isolation.

This study is expected to help answer questions such as: Is the family a significant site for spread of virus? Is the school age child an index case for spread of disease (and hence a vaccine target)? What is the clinical description of the disease by age group? What is the duration of immunity from natural disease?

Vaccine Research and Development. Influenza vaccines presently approved for use are inactivated (killed) preparations made from strains causing disease in humans. Each year, due to genetic drift (as explained earlier) the vaccine must be changed and, during an epidemic year, the necessary change may be so drastic that manufacturers find it difficult to get an effective product on the market quickly enough to reduce the number of illnesses and excess deaths.

In addition, the effectiveness of inactivated vaccines has been variable and protection relatively brief. Routine use of influenza vaccine is recommended only in the military and in chronically ill and aged populations. There is a need, therefore, for better influenza vaccines which could be manufactured promptly to handle new virus strains and would be useful in immunizing all age groups.

A number of NIAID scientists, grantees, and contractors are engaged in this area of research and development, and different modalities are being explored. These include (1) live vaccines made from temperature-sensitive mutants of the influenza virus, (2) inactivated recombinant vaccines specific for only one of the two major antigens of the influenza virus, and (3) inactivated purified protein subunit vaccines.

Live Vaccines. For several years, scientists in NIAID's Laboratory of Infectious Diseases (LID) in Bethesda, Md., have been evaluating temperature-sensitive (ts) mutants of the influenza A virus for their safety in man and for their suitability for use as live virus vaccines. These mutants are obtained by chemically treating cultures of influenza A virus and then selecting out those altered viruses that are restricted in growth at certain temperatures. Influenza mutants with greatest potential for use as live vaccines are ones that cannot grow in the warmer temperatures of the human lower respiratory tract (where they might cause serious disease) but will grow in the cooler temperatures of the nose and throat (where they can induce the formation of protective antibodies). The theory is that, by mating a suitably attenuated (weakened) temperature-sensitive mutant to a new wild-type influenza virus, it should be possible to produce rapidly an effective, attenuated, live vaccine to meet the challenge of a newly emerged strain.

Such prototype vaccines, developed by LID's Chief, Dr. Robert Chanock and his co-workers, have been tested in laboratory animals, adults, and children. In animals and adults the vaccines were entirely satisfactory. They stimulated antibodies both in the blood serum and respiratory tract of volunteers and provided protection against wild type virus. However, when the vaccines were evaluated in very young children who had no antibody to either of the two major influenza virus antigens (hemagglutinin and neuraminidase), the recombinant ts mutant vaccines did not seem to be fully attenuated.

In studies at Children's Hospital, Washington, D. C., and Vanderbilt University, it was found that these double-seronegative children shed larger quantities of virus over a longer period of time than did children who had detectable antibody to one of the antigens -- neuraminidase. In addition, some double negative children developed a transient fever and had symptoms of a mild upper respiratory infection. Although none of the vaccinees in the studies developed any signs or symptoms of lower respiratory tract involvement, wild type virus was recovered from the throats and nasal secretions of some of the double seronegative children.

These findings are of major importance in planning vaccines for use in the event of another pandemic. If the next major shift in the virus involves both the hemagglutinin and neuraminidase antigens -- as happened in 1957 at the time of the Asian flu -- every member of the population will resemble the double seronegative child in lacking immunity to both surface antigens. NIAID efforts, therefore, are presently being directed toward development of additional ts mutant recombinants which might be more suitable for widespread use.

In other work with influenza A ts mutants, Dr. Chanock and his group have obtained strong evidence that it is, indeed, the ts lesion gene that specifies the level of growth restriction of a virus. Observations by the LID scientists that ts lesions themselves indicate growth restriction -- or attenuation -- have practical value. Scientists now know that ts mutants, when used as vaccine strains, can be monitored directly for attenuation during all stages of vaccine development, manufacture, and usage.

An Inactivated Recombinant Vaccine. In other experimental vaccine studies, an inactivated recombinant preparation specific for the neuraminidase surface antigen alone is currently being evaluated for safety, antigenicity, and efficacy. Last year Dr. Pearay Ogra, Children's Hospital, Buffalo, N. Y., vaccinated 400 school children, ages 9-14, with this monospecific vaccine. Four hundred other children received the conventional vaccine or a saline placebo. Dr. Ogra is now evaluating his data to see what protection was afforded by the vaccine in the face of an outbreak of influenza in Buffalo last winter.

The vaccine virus used in this trial, and in earlier ones at Baylor, was a "tailor-made" hybrid developed by Dr. Edwin D. Kilbourne, Mt. Sinai School of Medicine. Dr. Kilbourne, whose work has been supported by grants from NIAID, constructed the virus vaccine from hemagglutinin of a horse influenza virus and the neuraminidase of a human virus. Adult volunteers receiving this vaccine develop relevant immunity only to the neuraminidase component and, when exposed to wild type virus, seem to be protected against illness, although infection takes place.

Subunit Vaccines. To prevent toxic reactions to inactivated influenza vaccines containing intact virus particles, it has become standard procedure to use ether or detergents to disrupt the viruses. Such disrupted vaccines still contain, however, internal components of the virus which play no role in the stimulation of protective antibody but do cause trouble in some vaccinees, particularly children. This problem is being tackled by a number of investigators who are interested in making vaccines out of isolated components of the virus.

In a pilot study of one of these vaccines, called HANAFLU, Baylor investigators found that, in man, the experimental vaccine was as immunogenic as the whole virus. HANAFLU, prepared by Dr. Webster of St. Jude, contained purified

hemagglutinin and neuraminidase from the Port Chalmers strain of type A influenza virus. A vaccine made from the newer Scotland strain is now being tested in seronegative volunteers. Responses to varying doses of these and other investigational subunit vaccines will be examined by Baylor scientists and, eventually, clinical effectiveness of the preparations will be assessed by challenging the vaccinees with wild type virus.

Immunology. Closely related to vaccine development is the need for definitive data on protective mechanisms and correlates of influenza immunity. Various aspects of the immunological response to live and inactivated influenza vaccines are being studied by a number of investigators. For example, Baylor scientists have described a modification of a lymphocyte-mediated cytotoxicity test used for rubella and measles viruses which can be used to test, in vitro, the cell-mediated response to influenza virus. The Texas scientists plan to obtain white blood cells from both seronegative and seropositive volunteers and to test these cells for lymphocyte cytotoxicity -- an indicator of cell-mediated immunity.

A clearer understanding of the relative roles of the two forms of the immune response -- humoral, as expressed through antibodies, and cell-mediated as evidenced by other components of the immune system -- should enable scientists to devise better ways of protecting against and treating influenza infection. Recent research by NIAID intramural scientists has indicated that three antigenic variants of the Hong Kong flu virus, isolated in different years and in different geographic locations, are similarly sensitive to the naturally occurring protective substance -- interferon -- a product of cell-mediated activity.

Respiratory Syncytial Virus, Parainfluenza Viruses, and Adenoviruses

In addition to influenza, other viruses causing acute respiratory disease include respiratory syncytial, parainfluenza, and adeno.

Respiratory Syncytial Virus. Since its initial isolation from infants with respiratory disease nearly 20 years ago, respiratory syncytial virus (RSV) has emerged as the major agent causing lower respiratory tract disease in infants and young children. This virus presents a special challenge to scientists since it exhibits an unusual pattern of infection and disease. In spite of intensive research, many pressing questions concerning the development of serious, life-threatening RSV disease of the lower respiratory tract during early infancy remain unanswered.

A number of epidemiologic studies have documented the prevalence of this disease agent during early childhood. For example, in a 13-year surveillance of infants and young children admitted to the Children's Hospital of D.C. with lower respiratory tract disease, RSV infection was detected in 43% of those admitted with the diagnosis of bronchiolitis, and in 25% of patients with pneumonia. In contrast, RSV infection was detected in only 5.4% of infants and children seen in the clinic or admitted to the hospital for non-respiratory illness during this interval.

It is probable that RSV infection is even more widespread than such surveys indicate. Cell cultures commonly used for the recovery of RSV vary in their sensitivity to the agent and at times may be completely resistant. Then, too, blood tests for the detection of infection are comparatively inadequate when very young infants are study subjects. Evidence indicates, however, that the virus becomes widely disseminated during each yearly epidemic and that the risk of infection for previously uninfected young children is extremely high.

Because of the importance of RSV infection in early childhood, scientists have been attempting for nearly ten years to develop an effective vaccine. Difficulties were encountered with an early inactivated vaccine, which stimulated the induction of high levels of antibody in the blood but did not prevent disease.

This experience, plus the observation that naturally acquired RSV infection does confer protection against repeated infections, has led NIAID scientists and others to attempt to develop an attenuated strain of live RSV for use as a vaccine.

Interest has focused on ts mutants chosen (like their influenza counterparts for their ability to grow in the cooler temperatures of the upper respiratory tract but not in the warmer regions of the bronchus and lungs. In adult volunteers and older children, one mutant, ts-1, did not produce disease, was protective against challenge with wild type virus, and was genetically stable -- that is, did not revert to wild type. However, when the vaccine was administered to younger children and infants, it was found to retain a small amount of residual virulence and to be unstable genetically, as indicated by the shedding, by some vaccinees, of genetically altered virus with temperature sensitivity characteristic of the wild type virus.

The search is on, therefore, for more attenuated strains of RSV which might also be more stable. Scientists in NIAID's Laboratory of Infectious Disease and NIAID contractor, Dr. Robert Simpson, Rutgers University, have been developing "double" mutants for RSV. These are viruses that have two genetic defects and, thus, are less likely to revert to their original form.

Work with these double mutants was temporarily slowed during the year by Dr. Simpson's discovery that RSV can enter into association with host cells in the form of a proviral DNA intermediate. This finding suggested a need to reevaluate the concept of live virus vaccines if virus genetic material persisted in human cells.

To consider this and other problems of viral persistence, a workshop was organized by NIAID's Infectious Disease Branch and the Bureau of Biologics, Food and Drug Administration. This meeting, held in October 1975, was attended by nearly 50 experts in virology and vaccine development. The workshop participants concluded that concern about persistence of vaccine viruses might be unjustified since long-term immunity itself may be dependent on persistence of virus or virus antigen.

In regard to use of ts mutants, the scientists further observed that the Sabin polio vaccine and the measles vaccines -- two of the most valuable and widely utilized live virus vaccines -- are temperature-sensitive mutants. In the development of an RSV vaccine -- as in all vaccine development -- the scientists felt that potential risks should be carefully weighed against potential benefits.

Valuable information regarding RSV is expected to be forthcoming from experimental animal models now under development. Two NIAID contracts have been awarded for these models and work with the ferret has been particularly encouraging. Scientists at the University of California, Los Angeles, working under Dr. David Porter have confirmed an earlier finding that organ cultures of ferret lung and trachael rings can be infected with RSV. The scientists have also found that washed macrophages (scavenger cells) from immunized adult ferrets inhibit RSV replication in the cultures, indicating, perhaps, that protection from RSV infection may be dependent on maturation of the macrophage.

Parainfluenza Viruses. Members of this family of viruses are a common cause of pharyngitis, bronchitis, croup, and bronchopneumonia in children and an occasional cause of upper respiratory infection in adults. Croup caused by parainfluenza virus is very severe and occurs most frequently between the ages of 1 and 4 years.

In an attempt to develop a suitably attenuated virus for use in a vaccine, NIAID-contract supported scientists have isolated 14 ts mutants of type 3 parainfluenza in primary cell cultures from chemically mutagenized stocks of virus. Studies of these mutants in hamsters are continuing to determine attenuation,

genetic stability, and lack of persistence in mammalian cells. Mutants to types 1 and 2 parainfluenza viruses will also be derived.

In other parainfluenza research, a NIAID-supported group at Vanderbilt University, Nashville, is engaged in a clinical trial of attenuated live vaccines developed by Merrell-National drug company against types 1 and 3 parainfluenza. The Vanderbilt scientists will study the effect of intranasal administration of the vaccines to normal children aged 12 to 36 months. These preparations have previously been found safe in older children and adults.

Adenoviruses. Although there are over 30 types of adenoviruses, only certain ones are highly prevalent causes of infection in man. Types 4 and 7 are responsible for a great deal of respiratory illness in the military while types 1, 2, 3, and 5 are highly significant causes of acute respiratory disease, including pneumonia, in infancy and childhood.

Effective vaccines have been developed for adenovirus types 4 and 7 and have been used successfully in the military. The vaccination procedure consists of swallowing a coated capsule containing live adenovirus. The respiratory tract is bypassed, intestinal infections without symptoms occur, circulating antibody is formed, and a high degree of resistance develops.

Alternative approaches to vaccination for adenovirus disease include use of injected inactivated virus preparations. Use of these was stopped when, several years ago, injected adenoviruses were found to be tumor-producing in newborn hamsters. This oncogenic property was later shown to be a function of the viral nucleic acid and, while recent studies have failed to support a role for adenoviruses in human tumor formation, this finding remains a point of concern.

New methods for crystallizing surface subunits of the adenovirus have been developed recently and have provided the opportunity to immunize individuals by the parenteral (injection) route with preparations completely free of nucleic acid. Moreover, such preparations have no detectable non-viral proteins, a feature which generally cuts down on adverse reactions such as pain and inflammation at the site of injection.

Subunit vaccines for type 5 have been prepared and found safe and antigenic (capable of inducing protective antibodies) in adults and teenagers. During the past year they were evaluated in children by investigators at the Baylor College of Medicine. The 10-15 age group was studied first, then 5-10 year olds. Although results were satisfactory in these groups of children, there was a low frequency of response in 3 to 5 year olds. Dr. Robert Couch and his associates are now administering a booster injection of the subunit vaccine to see if a higher titer of serum neutralizing antibody can be obtained in these young children who are at greatest risk of serious respiratory disease.

For some years Dr. Maurice Green, St. Louis University, has been monitoring both normal tissues and tumors from man for the presence of DNA (nucleic acid) sequences specific for adenoviruses 2, 4, 7, and 12. To date he has found no evidence for the presence of viral DNA in tumor tissue. Dr. Green's contract is funded through the Bureau of Biologics, FDA, with a portion contributed by NIAID because of the Institute's past and possible future interest in whole adenovirus vaccines.

Mycoplasma Pneumoniae

Although mycoplasmas -- the smallest of free-living organisms -- are found in many species of plant and animal life, only one -- M. pneumoniae -- is known to cause disease in man. Frequently isolated from the nose and throat of children, M. pneumoniae causes disease most often in teen-agers and young adults -- particularly those housed in close quarters, such as military recruits.

More than fifteen years ago, it was established that M. pneumoniae was susceptible to treatment with antibiotics. It was soon discovered, however, that, while this treatment shortened the duration of fever and the acute phase of the pneumonia, symptoms such as cough and malaise often continued for weeks. Even more important, antibiotic therapy failed, in most instances, to eradicate M. pneumoniae from the respiratory tract, and shedding of the organism often continued for a prolonged period.

For these reasons, investigators turned to the development of effective means for preventing mycoplasma pneumonia. Inactivated vaccines were first developed and a number tried over the years. Results, in general, have been disappointing. For example, NIAID has been supporting the development and testing at the Parris Island Marine Corps Recruit Camp in South Carolina of an inactivated M. pneumoniae vaccine -- OSU-1.

Preliminary evidence indicates that the vaccine given to over 3,500 volunteers was only about 40-50% effective in preventing M. pneumoniae pneumonia. However, not all serologic data are in. Until antibody studies are done, it will not be possible to state precisely the rate of protection afforded by the OSU-1 vaccine.

It seems likely, however, that some means other than inactivated vaccines will be needed if mycoplasma pneumonia is to be prevented in groups at highest risk. NIAID interest is focused, at present, on the work of Dr. Chanock and his group in Bethesda, Md., where these scientists have been working for several years with live attenuated mutants of M. pneumoniae which, introduced into the nasal passages, stimulate local immunity. These are temperature sensitive mutants like those produced for influenza and respiratory syncytial virus.

After tissue culture and animal studies, two of these mutants have been evaluated as candidate vaccine strains in small groups of volunteers. One, mutant ts 640, was given to 11 men intranasally. The mutant was genetically stable, but caused some illness. Mutant ts H43 did not infect hamsters and it was thought that it would be over-attenuated for humans. However, when given intranasally to volunteers with no evidence of previous M. pneumoniae infection, H43 induced a high titer of antibody in 97% of 35 men and produced a four-fold rise in antibody in 79% of 19 volunteers who were initially positive for previous infection.

Since the H43 vaccine did, however, produce mild bronchitis without fever in 4 of the 54 volunteers, it is still considered an experimental vaccine only, not ready for clinical application. At present, Dr. Chanock and his co-workers are carrying out studies to determine the minimal dose which would be protective but would eliminate bronchitis by using lower concentrations of the organism.

The NIAID investigators did note, however, that in none of the volunteers receiving the H43 vaccine was there any evidence that cell-mediated immunity to M. pneumoniae had been invoked. Since a number of studies have suggested that this form of the immune response may actually be involved in the development of clinical disease, the failure of ts-H43 to stimulate cell-mediated immunity suggests that this vaccine may be more useful than expected in preventing M. pneumoniae disease.

Streptococcus pneumoniae

Pneumococcal pneumonia, caused by Streptococcus pneumoniae, (formerly called Diplococcus pneumoniae), remains a serious disease. In spite of the availability and use of effective antibiotics, a 20 to 30 percent fatality rate of patients hospitalized with pneumococcal pneumonia has remained unchanged over the past decade.

For this reason, NIAID initiated several years ago, trials of vaccines containing more than one type of S. pneumoniae. These polyvalent vaccines are made not from the organisms themselves but from the complex sugars, or polysaccharides, which compose the gelatinous capsules surrounding virulent forms of S. pneumoniae.

At present a large-scale trial is underway to determine the efficacy of a dodecavalent (12 types) pneumococcal vaccine in preventing type-specific pneumococcal pneumonia in adults over 45 -- a group at high risk of contracting this serious disease. More than 13,000 volunteers received either the vaccine or a placebo (inert preparation) in studies being carried out in San Francisco under a contract with Kaiser Foundation Research Institute.

The vaccines were well-tolerated by the recipients and a good serum antibody response to the antigens was seen. Persons taking part in the study will be followed for two years to see whether the vaccine was protective against development of pneumococcal disease. Dr. Robert Austrian of the University of Pennsylvania continues to act as consultant to all NIAID pneumococcal vaccine studies and the computer data base for the Kaiser study is maintained by him in Philadelphia.

In addition to pneumonia, S. pneumoniae is responsible for 40 to 50 per cent of cases of otitis media in children. Acute otitis media -- inflammation of the middle ear -- is a serious disease of young children, affecting all racial groups and social classes.

In order to assess the possibility of using one of the pneumococcal vaccines in children at high risk for otitis media, NIAID first awarded a contract to investigators at the University of California, San Francisco. In their study, no adverse reactions were observed in any of the children, and a good antibody rise was seen in all over 2 years of age. Infants under a year were found in this study, as in others, to respond less well to pneumococcal antigens.

Since these results seemed to indicate that the pneumococcal vaccine might be useful in children, particularly those at high risk to otitis media, two contracts have been awarded by NIAID for evaluation of the preparations in infants. One will be carried out at Boston City Hospital and the other in Huntsville, Alabama. In addition, scientists at Vanderbilt University will carry out studies to determine the optimum vaccine dose and booster regimen for maximum antibody production in infants.

A contract to develop an animal model for the study of pneumococcal otitis media has been awarded to the University of Minnesota. This work, under the direction of Dr. Paul Quie, will focus initially on the use of the chinchilla -- a small animal with very large ears on whom auditory tests can be performed.

Vaccine Evaluation Centers

Over the years a number of institutions have served as general vaccine evaluation centers for work sponsored by the NIAID. At present five such centers* are under contract and some of their work has already been mentioned in this report.

Of particular interest is a new study at the center at the University of Rochester's Strong Memorial Hospital. Scientists there are exploring the role of respiratory viruses in causing hospital-acquired infections. A number of earlier investigations have suggested that such infections, particularly among children, may constitute a problem of some magnitude.

Accordingly, all young children and infants admitted to the children's wards at Strong Memorial Hospital during a community outbreak of one of the respiratory viruses will be studied, along with ward personnel. The presence of these viruses in the community will be identified by means of an ongoing surveillance system and by virus isolation in the hospital's diagnostic laboratory.

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*D.C. Children's Hospital, Washington; University of Colorado, Denver; Vanderbilt University, Nashville, Tennessee; University of Rochester, N. Y.; and Baylor College of Medicine, Houston, Texas.

Drs. Caroline B. Hall and R. Gordon Douglas at the Rochester center expect the study to delineate the frequency of viral nosocomial (hospital-acquired) infections, their significance in terms of illness, mode of transmission, and, subsequently, possible methods of prevention.

BLACK LUNG DISEASE (COAL WORKERS' PNEUMOCONIOSIS)

Black lung disease, or coal workers' pneumoconiosis, is an incapacitating, life-shortening constellation of disease processes caused by the inhalation and retention in the lungs of coal and other mine dusts.

Black lung benefits paid under the provisions of the Federal Coal Mine Health and Safety Act total $77.5 million per month. Recipients of these benefits include 173,000 miners, 139,400 widows of miners, 2,700 other surviors, and 190,700 dependents of miners.

Black lung disease kills more Americans than all other forms of pneumoconiosis (the various dust-inhalation diseases) combined, and afflicts approximately 100,000 Americans. Though it may be prevented through methods of minimizing exposure to dust, the disease is irreversible once established.

Thus, complete control of black lung disease in this country requires extensive application of preventive measures, and continuing basic and clinical research to learn where and how we may intervene to slow or halt the progression of the underlying disease processes.

Obligations for Black Lung Disease (Coal Workers' Pneumoconiosis)

	1973	1974	1975	1976 Estimate	1977 Estimate
Public Health Service:					
Center for Disease Control National Institute for Occupational Safety and Health	$5,317,000	$8,483,000	$4,300,000	$4,717,000	$4,800,000
National Institutes of Health National Heart and Lung Institute	163,000	200,000	250,000	250,000	250,000
Total	$5,480,000	$8,683,000	$4,550,000	$4,967,000	$5,050,000

CENTER FOR DISEASE CONTROL

National Institute for Occupational Safety and Health

Activity Under the Federal Coal Mine Health and Safety Act of 1969 (P.L. 91-173)

Under Public Law 91-173, the Federal Coal Mine Health and Safety Act of 1969 (as amended by P.L. 92-303), the Secretary of Health, Education, and Welfare conducts programs dedicated to improving the health and protecting the lives of coal miners and others whose work requires proximity to the products of coal mines. The law authorizes the operation of clinical facilities for analyzing and treating respiratory and pulmonary impairments in miners, and provides for major investigative and research efforts devoted to the prevention and early detection of respiratory diseases in coal miners. Operational authority for meeting these responsibilities has been delegated to the National Institute for Occupational Safety and Health (NIOSH), whose mission, with regard to the Federal Coal Mine Health Safety Act of 1969, is to ensure that the coal miner performs his work under conditions that are as safe as possible to his health.

NATIONAL STUDY OF COAL WORKERS' PNEUMOCONIOSIS

The National Study of Coal Workers' Pneumoconiosis began in August 1969, prior to the enactment of the Federal Coal Mine Health and Safety Act of 1969. The purposes of the study are (1) to relate coal workers' pneumoconiosis (CWP) or black lung disease progression to levels of respirable dust exposure, (2) to provide a scientific basis for determining the progression of the disease by use of serial x-rays, and (3) to estimate the industry-wide prevalence of CWP.

The miners are examined at each participating mine by medical teams for NIOSH. Each examination includes an occupational history, two standard chest x-rays, a simple test of lung function, and a short questionnaire on chronic bronchitis developed by the Medical Research Council of Great Britain.

The miners were chosen for the Study to represent varying geographic regions, coal seams, and mining methods. Because the Study involves monitoring miners' health at 3 to 5 year intervals, mines with an expected working life of at least ten years and which employed at least 100 miners were chosen. An effort was also made to choose mines for which prior dust exposure information is available.

The first round of the Study, comprised of examination of 9,076 miners at 31 mines, was completed in 1971. This study showed that approximately 30 percent of all miners tested had pneumoconiosis. The second round of the Study, completed in 1975 and comprised of examinations of 9,073 miners, showed that approximately 10.8 percent of all miners tested have had pneumoconiosis. Presumably the improvement in prevalence figures is due to a combination of the benefits of environmental controls and the influx of new miners. Approximatley one-half of the men examined in the first round were not examined in the second. Many older men retired and some left the mining industry because of disability or other reasons. Often they have been replaced by young men who have not been exposed to coal mine dust.

COAL DUST INHALATION STUDIES

NIOSH toxicologists have continued laboratory studies of experimental animals. In one study, cynomolgus monkeys were exposed to chronic inhalation of two types of bituminous coal dust - a Pennsylvania coal dust found in an area where workers suffer a high incidence of pneumoconiosis, and a Utah coal dust from an area in which a low incidence of pneumoconiosis has been recorded. In these studies, toxicologists maintain detailed records of any changes in the monkeys' pulmonary functioning. The animals are exposed to coal dust in concentrations of two milligrams of respirable dust per cubic meter of air (2 mg/m3), the current Federal maximum allowable standard for underground coal miners. The ultimate

objective of this research is to determine whether the current dust exposure standard is adequate or in need of revision.

In 1976 the NIOSH proposes to develop mandatory health standards, preventive examination programs, and protective engineering techniques in an effort to assure that coal workers are provided a working environment which will prevent occupationally caused diseases.

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

The National Heart and Lung Institute bears primary responsibility for basic and clinical research concerned with the respiratory system and with developing improved methods for the prevention, diagnosis, and relief of chronic lung diseases (other than the infectious and malignant lung disease, which are the provinces of the National Institute of Allergy and Infectious Diseases and the National Cancer Institute, respectively).

In partial accomplishment of this mission, the NHLI Division of Lung Diseases spent $400,000 in FY 1975 in support of four regular research grants and five sub-projects within Specialized Center of Research (SCOR) pulmonary programs for research on certain of the pneumoconioses. This is a collective term for a number of different diseases caused by the inhalation and retention in the lungs of mineral or vegetable dusts and including such diseases as silicosis, asbestosis, byssinosis, and--the subject of this report--coal workers' pneumoconiosis, or black lung disease. Approximately $250,000 was spent for research directly on black lung disease.

Magnitude of the Problem

Black lung disease is believed to account for more deaths--approximately 1,000 per year in this country--than all other forms of pneumoconiosis combined, and afflicts an estimated 90,000 to 125,000 miners. According to a 1967 report by the Pennsylvania Department of Public Health, 43,000 Pennsylvania coal miners had X-ray evidence of coal workers' pneumoconiosis and more than half of these (nearly 24,000 miners) were disabled by it. A recent nationwide survey by the Public Health Service and the Bureau of Mines indicates that nearly 30 percent of working coal miners in the U.S. have black lung disease.

It takes a decade or more of exposure to mine dusts before miners are incapacitated or killed by the disease. In the interim, they experience progressively severe wheezing, coughing, and shortness of breath, and increased susceptibility to colds and other respiratory infections, including tuberculosis.

Black Lung: A Composite of Several Disorders

The progressive, irreversible nature of the disease is revealed by autopsy examination of lung tissues following varying periods of exposure to the mine dusts.

This also shows that the disease actually involves five or more different disease processes.

- Some of the inhaled dusts are retained and become permanently incorporated into the walls of the small air passages (bronchioles) and sacs (alveoli) to form microscopic, focal deposits called macules. In aggregate, these macules are grossly visible as blackened patches and streaks in lung slices even following only a few years of dust exposure.

- Destruction of lung tissue around the dust deposits produces a halo of emphysema--in effect, a dead air space--around each macule.

- In some patients, scar tissue formation (fibrosis) occurs between macules, and can involve large areas of the lung. While the occurrence and severity of fibrosis are unpredictable, fibrosis has been associated in some studies with exposure to silica dust,

and in others with tuberculosis.

- The eventual development of chronic bronchitis and the more generalized forms of emphysema contribute importantly to shortness of breath and disability in coal workers' pneumoconiosis.

- Finally, many afflicted workers exhibit as a complication of their disease elevated blood pressure in the lungs (pulmonary hypertension) and, as a consequence of this increased pressure, compensatory enlargement of the right side of the heart.

Heart failure is the most common cause of death in persons with black lung disease; many others succumb to respiratory failure during an acute respiratory infection.

Treatment

There is no form of treatment that will halt, much less reverse, the slow course of black lung disease. Available therapy is aimed either at complications of the disease, or at relieving some of its symptoms. Antibiotics are used to treat respiratory infections, and cardiotonic drugs enable the heart to pump more blood through remaining lung tissue. Also available are a number of drugs to ease breathing by dilating air passages or by dissolving obstructive mucus secretions. Research continues on other ways of ameliorating the symptoms and complications of black lung disease.

Prevention

Prevention is the only known way of controlling black lung disease and, as studies in Great Britain have demonstrated, is quite effective. This is accomplished by reducing dust levels in working environments, and limiting the duration of exposure to dust. Specific measures include the use of dust monitoring systems, wetting practices, air filters, dust masks and other equipment to collect or suppress dust at its source or remove it from the atmosphere, improved ventilation systems, rearranging work shifts to reduce individual exposure to particularly dusty environments, periodic X-ray examinations and pulmonary function tests to detect the disease in its early stages, and other screening tests to identify job-applicants and others who might be especially susceptible to the disease. People with an hereditary deficiency of the enzyme alpha-1-antitrypsin are more likely to develop black lung disease in a particularly severe form in terms of both earlier onset and relatively more rapid progression of the disease. And, for reasons as yet unknown, workers who have either tuberculosis or rheumatoid arthritis together with black lung are especially prone to develop massive pulmonary fibrosis.

Finally, anti-smoking campaigns and above-ground air pollution control activities are (or should be) important elements of any effort to control black lung disease. Additional airborn insults to the lungs aggravate the symptoms and accelerate the course of the disease.

In Great Britain, where coal workers' pneumoconiosis was first described and control measures initiated 30 years ago, mortality and disability rates from black lung have been halved. Complete control of the disease in this country, including help for those who already have black lung, requires extensive application of known preventive measures and the acquisition of new information concerning the underlying disease processes.

Current Research Efforts

Research is being pursued in NHLI grant-supported studies of black lung disease. One study, conducted by Dr. Richard L. Naeye at the Pennsylvania State

University School of Medicine, Hershey, is a combined clinical-epidemiological-pathological investigation of the five or more disease processes that constitute coal workers' pneumoconiosis. This comprehensive project includes autopsy studies of 500 coal workers, 300 miners' wives, 650 people not associated with the coal mining industry and 400 rural Pennsylvanians matched for age and race with the other groups. Though not completed, this study has yielded interesting preliminary findings correlating types and severities of disease manifestations with exposure to coal dust at different mine sites and in soft and hard coals.

Dr. Naeye's research team has also developed a very sensitive test system for investigating the role of immunological defense mechanisms in black lung disease. There is some clinical and autopsy evidence that sensitization and subsequent exposure to any one of a number of antigenic substances (bacteria, fungi, organic and inorganic dusts, etc.) may be involved prominently in some cases of black lung, even perhaps in the early stages of the disease. The test, a modification of the lymphocyte transformation test, reveals immunological responses of cultured white blood cells to even very low levels of antigens, such as might be found in the respirable dusts of mine air samples.

The investigators have just begun to apply the test, obtaining blood samples from coal miners in various mining regions, isolating and culturing the lymphocytes and challenging these cells with respirable dust samples (supplied by the Bureau of Mines) and with specific antigens including beryllium, purified protein derivative (PPD) of tubercle bacillus culture, and certain fungal antigens known to be present in some mines. Eventually, the studies will include additional organic compounds as these are isolated and identified from mine dusts by Bureau of Mines chemists in Pittsburgh.

Similar research questions are begin pursued by Dr. Russell A. Harley, Medical University of South Carolina, Charleston. His studies in animals are testing the hypothesis that progressive massive fibrosis of the lungs (PMF), one of the most dramatic possible consequences of black lung disease, is the result of an altered inflammatory response of lung tissue caused by an induced hypersensitivity. This hypersensitivity is thought to be accentuated by adsorption of antigen to the stored dust in the lungs, which prevents the destruction of the antigen and favors prolongation of its activity.

Dr. Harley and co-workers found that guinea pigs sensitized with histoplasmin or with tubercle bacillus antigens developed a persistent chronic inflammatory reaction involving the alveolar wall in response to subsequent exposure to the appropriate antigen alone. But when pre-sensitized animals were given massive doses of coal dust along with the antigen, massive lesions containing trapped dust and fibrosis (connective tissue, or scarring characteristic of early PMF) were produced. The PMF guinea pig lung has many of the gross and microscopic features of the human disease in its early stages, including the diffuse distribution of fine coal dust and the uniformly black pigmentation of the lung.

The studies are incomplete, but the finding that massive amounts of dust are required for the development of PMF in experimental animals suggests that even moderate reductions in exposure to mine dust may effectively prevent the development of this dread complication of black lung disease in humans.

Microscopic studies of the guinea pig lesions suggest that hypersensitization by pre-exposure to antigens is another important link which, if broken, may allow eventual removal of inhaled coal dust via natural clearance mechanisms. In this animal model of black lung disease, alveoli collapse around the dust-containing macrophages. Inflammation and fibrosis then stiffens and locks these alveoli in the collapsed position, thus permanently trapping dust within them.

BURN RESEARCH

The National Institute of General Medical Sciences (NIGMS) has continued and intensified its efforts in the support of research on burn injuries. In addition the NIGMS has cooperated with the Health Services Administration and other health agencies in order to develop an effective program in burn research and care.

Obligations for Programs in Burn Research

	1973	1974	1975	1976 Appro.	1977 Estimate
National Institutes of Health:					
National Institute of General Medical Sciences	$1,000,000	$2,100,000	$2,700,000	$4,000,000	$5,000,000
Health Resources Administration:					
Bureau of Health Manpower:					
Nursing Special Projects	---	---	118,492	100,000	---
Health Services Administration	1/	1/	1/	1/	1/
Total	$1,000,000	$2,100,000	$2,818,492	$4,100,000	$5,000,000

1/ Obligations not identifiable

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

I. Research Activities Supported by NIGMS

A. Background

Each year approximately 70,000 people receive burns which are serious enough to require intensive care. Despite the excellence of this care, almost 10,000 die from either early undefined biochemical and physiological changes or from latent fulminating infection. Twenty-nine percent of seriously burned children under 15 die as a result of burn injuries and, generally, deaths in males outnumber those in females. The health-related cost to the nation is $300 million annually. Further, a severe burn injury is one of the greatest emotional and physical handicaps known.

It is, therefore, evident that the management of severe burns (defined as involving 30 percent or greater of the total body surface) still is a critical problem. Although there are effective means of treating the acute shock phase by judicious intravenous fluid replacement and other supportive measures, this has not been associated with a decrease in the overall mortality. Rather, there has been a shift in the time of death, so that many of those who survive the initial crisis subsequently die from overwhelming infections or from pulmonary or renal complications.

Recently, a concerted effort in research on burn injuries has led to the development of more specific forms of treatment, with some increased success in treating such complications. However, continued research is needed to understand completely the complex problems related to burn injury. For instance, little is known about the relationship of the development of infection to host resistance, or about the reasons why abnormal immunological responses develop in burn victims and thus affect the acceptance of skin grafts, the most important method of repair of burned skin. Furthermore, there is preliminary suggestive evidence that there is release of toxic materials after thermal injury. Investigators are currently studying these newly isolated compounds.

B. Research Accomplishments

In FY 75, the NIH supported burn research in the amount of $3.2 million. Of this, $2.7 million was the research effort of the Trauma and Burn Research Program of the National Institute of General Medical Sciences. The mission of this program is to provide a better understanding of the mechanisms leading to death and disability from accidental injuries, through support of research. Such studies on cellular and molecular changes should provide important information as to why organs fail, and should help to define the body's total response to injury. In order to increase survival rate, the recognition of organ failure must occur at a time when it is reversible. The establishment of burn research centers has provided a mechanism for rapid clinical application of new knowledge gained from basic laboratory studies.

For example, at the University of Cincinnati burn and trauma research center, Dr. William Altemeier and his associates have found that the indiscriminate use of antibiotics in burned patients has caused the normal skin bacteria to change into forms which are more resistant to most types of therapy and cause an overwhelming infection. In another study on burn patients, this same team has devised a test to determine the loss of ability of the patient's white blood cells to kill bacteria, thereby permitting the clinician to predict impending infection.

The first center devoted totally to burn research was activated by NIGMS in June 1974, under the direction of Dr. John Burke at the Massachusetts General Hospital. Through research efforts, the investigators have found some of the necessary sequential steps for treatment of severe burns involving 80 percent of the total body surface with 70 percent being third-degree burns. The previous mortaility rate of 100 percent for such extensive burns has been reduced to 64 percent. The technique includes skin transplantation, immunosuppression, hyperalimentation, and a bacteria-controlled environment.

Fresh, tissue-matched skin is transplanted from parents, siblings, or other close relatives. The survival of these grafts is enhanced by the administration of immunosuppressive agents. To help combat life-threatening infections, the patient spends the most serious part of his illness (usually about three months) in a bacteria-controlled nursing environment. Increased metabolism demands an extraordinarily high calorie intake. Thus, hyperalimentation, a technique pioneered in part by these investigators, supplies the necessary amounts of calories, particularly as protein. During the four to eight week period of temporary skin grafts, autografting is being performed. When all but 20 percent of the burned areas have thus been covered by the patient's own skin, the immunosuppression is discontinued and grafts from cadaver skins are used to cover the remaining parts of the body. Reconstructive surgery is begun soon after removal from the bacteria-controlled unit. Usually the patient leaves the hospital six to seven months after admission. Unfortunately, considerable disfigurement still occurs.

The need for a satisfactory replacement for skin has become a critical problem in the treatment of severe burns. Over the last 15 years, active research has been carried out in an attempt to identify a synthetic material that might serve satisfactorily as a skin substitute. None of these materials has provided satisfactory skin function; and, although a number have been used clinically, no satisfactory clinical results have been achieved as yet. Very recently, these investigators at the Burn Research Center at the Massachusetts General Hospital, in collaboration with the Mechanical Engineering Department at Massachusetts Institute of Technology, have devised a method for the development of a composite synthetic material which has all of the biologic and physical properties of skin. The biomedical engineers applied the principles of materials development used in space technology. This collaboration has led

to the development of what is believed to be a very promising material that has many of the characteristics of skin. This artificial skin, made from animal tissues, is a composite of carbohydrates (starches and sugars) and protein fibers derived from cattle. These fibers are then coated with a second biologic material which protects them from being dissolved by naturally occurring enzymes. The fiber reinforcement makes the material strong; and when it is in place covering a burned area, it prevents the occurrence of fluid loss and infection--two of the most serious complications of severe burns. This is by far the most promising material that has been tested in animals as it does not produce inflammation or irritation and has not been rejected, allowing healing to take place.

In June 1975, NIGMS established a second burn research center at the University of Washington Harborview Hospital, Seattle. Studies at this center include the effects of smoke inhalation on metabolism, nutrition, and pulmonary function. Dr. P. William Curreri, director of this burn research center, has developed a precise formula which predicts the caloric requirements of these patients, based on body weight and on the percent of the body surface burned. Using this formula, he combined the needed intravenous concentrated sugar and protein solutions with the constant delivery of nutrients into the stomach via a nasogastric tube. This technique has made it possible to prevent weight loss in these patients throughout their entire hospitalization, whereas prior to the development of these extraordinary feeding techniques, patients with greater than 40 percent of body surface burns often had weight loss of up to 25 percent during the first eight weeks in the hospital. An acute weight loss of 30 percent is usually associated with death due to metabolic imbalance and, finally, severe pneumonia.

Presently, this therapy, along with more conventional treatment, has resulted in a better than 50 percent survival in young, adult patients with 85 percent total body surface burns. This represents a significant improvement over the prior experience of a mortality rate of 100 percent at both this research center and others throughout the United States.

The newly established burn center of 21 beds at the University of Washington's Harborview Hospital serves a four-state area known as the WAMI area (Washington, Alaska, Montana, and Idaho). Recently a pilot, who was severely burned over 80 percent of his body surface when his helicopter crashed and burned, was successfully treated by Dr. Curreri and his team. These investigators attribute the development of improved therapy to the many years devoted to the study of the basic pathophysiology of burn injury.

Other research centers in this program, although mostly involved in research on trauma, use burn patients in their studies. In addition, the Institute supports individual projects on burn research, which include studies on the mechanisms of cell damage or tissue changes following severe burns; the general biochemical changes caused by burns; the development of more effective skin grafts; topical therapy; control of sepsis; and, finally, the characterization of toxic substances released by thermal injury.

At the University of Texas Southwestern Medical School, Dallas, Texas, Dr. Charles Baxter, the project director, has found that, in patients with severe burns, complete replacement of the body fluids lost within the first 24 hours after thermal injury prevents severe metabolic changes and cardiac depression. Dr. Baxter has also found evidence, in patients in shock, of the presence in the blood of a chemical heart depressant. The amount of this substance is directly proportional to the severity of the burn, but it is not yet known whether its presence is unique in patients in burn shock. These preliminary studies suggest that the presence of such a factor may limit the effectiveness of resuscitation with fluids in the initial phase of burn injury.

In 1973, Dr. Charles Fox at the Columbia University College of Physicians and Surgeons developed silver sulfadiazine, which is now considered the most successful topical antimicrobial agent for the treatment of burns. This medication has been used in over 10,000 patients throughout the world and it has been found that its activity is not blocked by wound exudates or contaminants, that its broad action inhibits the growth of many bacteria and fungi, and that it does not cause allergic reactions. When applied to the burned surface, small amounts of silver are released over long intervals, thereby killing the bacteria. Less than 10 percent is absorbed, so that it is relatively nontoxic. Its effectiveness in conjunction with antibiotic therapy is indicated by the fact that at the Dallas Burn Center there have been only seven deaths in 315 patients with burn injuries involving up to 60 percent of the total body surface.

Mortality in patients with severe thermal injury may also be due to anoxia secondary to pulmonary complications. Although such anoxia has been linked to the inhalation of smoke and of incomplete products of combustion in a number of instances, the results of a study by Dr. Felix Rapaport at New York University suggest that early post-burn anoxia may be associated with release of showers of small blood clots into the lungs. It has been shown, further, that blood transfusions may cause such clots, and their formation may be prevented by the administration of heparin.

These are examples of studies that are providing important basic knowledge on burn injuries and their treatment. Deliberate planning in this field has permitted the Institute to support worthy research in needed areas. The following is a partial list of scientific areas which are of interest and importance to our program supporting burn research:

1. Cellular and molecular changes
2. Organ failure
3. Fluid and electrolyte changes
4. Smoke inhalation
5. Pulmonary response to nonthoracic burns
6. Response of endocrine glands
7. Role of infection and immune mechanisms
8. Use of skin grafts
9. Hyperalimentation
10. Psychosocial aspects

C. Training Program for Burn Research Activities

In June 1975, the Institute activated an institutional fellowship program in burn and trauma research under the new National Research Service Act. Seven institutional awards were made for the purpose of training physicians and scientists interested in research in these areas. The program uses a multidisciplinary approach, which is expected to advance our knowledge of the body's total response to injury and burns. These trainees are supervised by a staff that includes trauma surgeons and/or burn specialists, as well as basic scientists who provide research training in related fields, such as physiology, biochemistry, and microbiology. Six of the seven grants include research training on burns. In addition, six surgery training grants still active under the old research training program provide trainees with opportunities to perform studies in burn research; these programs will be phased out by 1977.

With an expanded program in support of burn research, the NIGMS expects to establish several new research centers in which multidisciplinary efforts can be brought to bear on the total burn problem, to provide funds for the training of more burn researchers, and to activate new research projects in uninvestigated areas. It is hoped that, through these efforts, the mortality rate from severe burns can be greatly reduced.

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II. Coordination with the Health Services Administration

The staff of NIGMS is working closely with the Health Services Administration on the development of an effective and comprehensive program. One member of the NIGMS staff serves on the Interagency Committee assembled by HSA to develop a plan for implementation of Section 19 of P.L. 93-498, Victims of Fires. The report of this committee will be completed by April 1, 1976. An outline of the areas the report will encompass is as follows:

NATIONAL BURN REPORT

1. Statement of Work - Summary of Congressional Mandate

2. Definitions -
   - o Types of burns
   - o Burn Program, Unit, Center
   - o Qualification of personnel for burn care

3. Needs -
   - o Describe the scope, magnitude, and geographic distribution of the current burn patient workload incidence
   - o Describe the personnel needs to adequately handle the workload to include training and education requirements
   - o Describe the areas requiring additional research to improve burn patient care

4. Resources -
   - o Describe the current facility resources to include distribution, patient stay, referral patterns, rehabilitation services
   - o Describe the personnel available to handle burn patients, to include education and training, number, geographic distribution, etc.
   - o Describe the usage of current resources to include occupancy, duration of stay, sources of transfer, etc.

5. National Burn Network -
   - o Describe the program plan for a national network for burn care to include
     - o Facilities distribution
     - o Training and education
     - o Research
     - o Time schedule
     - o Budget projection
     - o Existing legislative authorities

6. Recommendations -
   - o A comprehensive approach to a national burn capability and the legislative actions required

(Please see additional page for Timetable)

TIMETABLE FOR DEVELOPMENT OF
NATIONAL BURN NETWORK REPORT

Milestone	Date
1. Complete development statement of work.	December 1, 1975
2. Complete appointment of consultants for burn committee.	December 5, 1975
3. Complete preliminary outline of burn report.	December 12, 1975
4. Identify information and data sources to be used by Task Force, including types of information, definitions and other information details.	December 19, 1975
5. Meeting of Burn Task Force. Complete revised work plan. Develop detailed work assignments.	January 12, 1976
6. Meeting of Burn Task Force; report on completed work tasks.	February 17, 1976
7. Complete draft final report.	March 8, 1976
8. Meeting Task Force. Complete comments on draft final report.	March 15, 1976
9. Deliver draft final report to HSA for review and comment.	March 22, 1976
10. Complete final report and forward for approval.	April 2, 1976

To date this report is on schedule and will be submitted to the Senate by both the NIGMS and the HSA.

HEALTH RESOURCES ADMINISTRATION

Bureau of Health Planning and Resources Development
Burn Center Planning and Construction
Division of Facilities Development

The Hill-Burton program has always encouraged the development of new services which would render better health care and at the same time concentrate scarce health resources and skills. This is especially true of Burn Centers which have been given both planning assistance by Hill-Burton State agency and DHEW regional office staff and assistance by Hill-Burton funds on several occasions.

Public Law 93-641, signed on January 4, 1975, extended and extensively revised the Hill-Burton program. Burn Centers will be eligible under two types of formula grant assistance: (1) modernization of health facilities, and (2) construction of new inpatient medical facilities in areas which have experienced recent rapid population growth. The same facilities are also eligible for loans and loan guarantees with interest subsidy. A third type of grant assistance is project grants for construction and modernization projects designed to prevent or eliminate safety hazards in publicly owned medical facilities or to avoid noncompliance by such facilities and licensure or accreditation standards. The 1976 Appropriation contains $16.3 million for project grants, $57.9 million for formula grants (25 percent or more must be used for outpatient facilities), and nothing for new loan authority.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

HEALTH SERVICES ADMINISTRATION

Burn Centers

In response to the direction of Congress, given in its report on the DHEW appropriations for F.Y. 1976, and in light of the critical need for burn research and care centers across the country, the Health Services Administration has begun work to establish a plan and program for a network of Burn Centers. A Burn Task Force has been established and held its first meeting to outline its work schedule directed toward the joint report to be submitted to the Congressional Committee on Burn Centers. A preliminary outline of the report follows.

1. Statement of Work - Summary of Congressional Mandate

2. Definitions -
   - Types of burns
   - Burn Program, Unit, Center
   - Qualification of personnel for burn care

3. Needs -
   - Description of scope, magnitude and geographic distribution of the current burn patient workload - incidence
   - Describe the personnel needs to adequately handle the workload to include training and education requirements
   - Describe the areas requiring additional research to improve burn patient care

4. Resources -
   - Describe the current facility resources to include distribution, patient stay, referral patterns, rehabilitation services
   - Describe the personnel available to handle burn patients, to include education and training, number, geographic distribution, etc.
   - Describe the usage of current resources to include occupancy, duration of stay, sources of transfer, etc.

5. National Burn Network -
   - Describe the program plan for a national network for burn care to include -
     - Facilities distribution
     - Training and education
     - Research
     - Time schedule
     - Budget projection
     - Existing legislative authorities

6. Recommendations -
   - A comprehensive approach to a national burn capability and the legislative actions required.

HEALTH RESOURCES ADMINISTRATION

Health Manpower

Burn Centers

The Bureau of Health Manpower does not have an on-going program that relates to the categorical target of Burn Centers. However, the Division of Nursing has awarded a contract to the University of Texas, Southwestern Medical School which emphasizes educational training, instruction, and research of the burn phenomena to prepare nurses at the master's level of education to become experts in the care of patients suffering thermal injury.

CLINICAL IMMUNOLOGY: ALLERGY AND ORGAN TRANSPLANTATION

During the past five years, advances in research supported largely by the National Institute of Allergy and Infectious Diseases (NIAID) have defined the immune system as made up of white blood cells, bone marrow, thymus, lymph nodes, spleen, and elements of the liver. This organ is under genetic control and is the primary host defense mechanism against microbes, viruses, and other antigenic materials derived from the environment.

When the immune system is deranged, it is the fundamental cause of asthma and other allergies and contributes to the development of a long list of other diseases such as chronic glomerulonephritis, rheumatic heart disease, various forms of arthritis, lupus erythematosus, and disorders of the central nervous system. Deficiencies or derangements in the immune system are a consequence of genetic, medical, or environmental factors, or result, in ways still to be explained, from persistent microbial or viral infections.

Medically-induced immune system derangements are substantial problems, for example, in the use of powerful immunosuppressive drugs in cancer therapy, organ transplantation, and the treatment of a number of chronic disabling diseases. These derangements have led to susceptibility to infection by bacteria and fungi which are normally not a major medical problem.

NIAID has not only sponsored research which has delineated the immune system as one of the most important of the body. The Institute has also provided over the years support for development of immunologic tools being used to solve a variety of disease problems. For example, NIAID has been the primary source of support for research on techniques for matching tissues in organ transplantation and is now the major source of histocompatibility typing sera. Although these reagents were designed initially for use in organ transplantation, they are being applied also today in important studies on the relationship between certain histocompatibility antigens and susceptibility to specific diseases.

Obligations for Programs in Clinical Immunology: Allergy and Organ Transplantation

	1973	1974	1975	1976 Estimate	1977 Estimate
National Institutes of Health:					
National Institute of Allergy and Infectious Diseases	$10,095,000	$12,017,875	$12,018,521	$12,541,000	$14,425,000
National Eye Institute*	280,000	310,000	312,339	310,000	310,000
National Heart and Lung Institute*	3,900,000	4,407,000	3,000,000	3,000,000	3,000,000
National Institute of Arthritis, Metabolism and Digestive Diseases*	2,649,000	3,205,000	3,168,000	3,200,000	3,200,000
Total	$16,924,000	$19,939,875	$18,498,860	$19,051,000	$20,935,000

* Figures are for organ transplantation only.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Allergy

An allergy is, very simply, an altered bodily reaction to a substance (an allergen) which causes no reaction in a majority of the people. Frequently, these allergens are common substances -- foods, pollens, mold spores, insect venoms, house dust -- and their ubiquitous nature makes life miserable on a daily basis for an estimated 35 million Americans -- 17% of our population.

The response to these allergens results in production of blood proteins, or antibodies, which sensitize the individual to the allergic 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 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.

The mechanisms of the immune response in allergy are the proper province of immunology -- the science that deals with the phenomenon of immunity. Scientists supported by NIAID are elucidating the interactions of the various components of the immune response which alter the individual's reaction and lead to immunologically-mediated tissue damage. To hasten the translation of these laboratory findings into improved methods of treating allergic patients, NIAID established 17 Asthma and Allergic Disease Centers (AADC) around the country.

Mechanisms of the Allergic Response. Scientists are particularly interested in the mechanisms involved in the production of IgE. Levels of this sensitizing antibody in an individual's blood appear to be related to the intensity of allergic reactions. Dr. Gerald Gleich, director of the AADC at Mayo Foundation Graduate School of Medicine, Rochester, Minnesota, has found that ragweed-sensitive patients who have low levels of IgE have fewer and less severe allergic symptoms than those with higher levels. Consequently, Dr. Gleich is now investigating the effects of various drugs and immunotherapy, popularly called allergy "shots", on IgE levels in allergic individuals.

Using a test which measures the amount of IgE antibodies in blood, Dr. Gleich has found that he can predict which patients will benefit from a particular drug. For example, patients with high levels of IgE show a significant improvement when given the drug, cromolyn sodium, whereas patients with low levels of IgE do not respond to this particular drug.

Dr. Gleich has found that injections of pollen extracts, known as immunotherapy, suppress the rise in IgE antibodies which occurs in allergic individuals following the pollination season. In addition, as much as 40% of a person's IgE antibodies are formed in response to a specific antigen, such as ragweed pollen. This situation is quite different from that of other types of immunoglobulins or antibodies produced by the immune system where only 2 to 5% is directed against a specific antigen, such as a microorganism. These findings have encouraged Dr. Gleich to investigate newly accumulating data on the cellular mechanisms involved in the production of antibody.

Although T cells (thymus-derived white cells that are involved in the cellular types of immune response) have been recognized as important in a few allergies,

such as poison ivy, humoral antibodies produced by B cells (thymus-independent white cells) have been recognized as playing the major role in respiratory allergies such as hay fever. However, Dr. Kimishige Ishizaka, an NIAID grantee at Johns Hopkins University in Baltimore, showed several years ago that, in animals, T and B cells collaborate in the production of IgE antibodies.

Recently, the B cell production of antibodies to a purified ragweed antigen in humans has also been shown to require the collaboration of T cells. Drs. Raif Beha, Harvey Colton, an NIAID grantee at Children's Hospital Medical Center, Boston, and other scientists at Harvard Medical School mixed B cells from individuals sensitized to ragweed, the major culprit in hay fever, with culture fluid from T cells which had been exposed to ragweed antigen. This mixture resulted in the production of both IgE and IgG types of antibodies. The sensitized B cells alone did not produce antibody. These results clearly establish the helper role of T cells in human allergic antibody response.

Formation of IgE antibodies can be suppressed by another class of T cells which interfere with the interaction of helper T cells and B cells. Dr. Ishizaka was able to produce these suppressor cells in mice by repeated weekly injections of a chemically modified ragweed antigen. These injections are analogous to the immunotherapy injections which hay fever sufferers receive. Thus, it is likely that this form of therapy is effective because it generates suppressor T cells in the patients. Dr. Ishizaka is currently studying other ways to produce or increase suppressor T cells in the hope of providing a new approach to the treatment of allergic individuals.

Chemical Mediators. An exciting field of research on the allergic immune response centers around the action of chemical mediators which get other cells involved in the reaction. One mediator, ECF-A -- the eosinophil chemotactic factor of anaphylaxis -- was first identified by Dr. K. Frank Austen, director of the AADC at Robert B. Brigham Hospital of Harvard Medical School in Boston. ECF-A is known to be released along with histamine in allergic reactions in the lung and in nasal polyp tissue. This mediator has also been found in lung tumors, in the blood and urine of patients with lung cancer, and in the circulation when patients with cold-induced hives experience a severe local attack.

During the past year, Dr. Austen has determined the complete structure of ECF-A and succeeded in synthesizing it in the lab. This accomplishment should enable scientists to develop sophisticated tests for ECF-A and to elucidate its role in diseases in which the allergic type of immune response is involved. It appears that ECF-A limits the allergic reaction by attracting cells called eosinophils, which, in turn, inactivate other chemical mediators, possibly including histamine and slow reactive substance of anaphylaxis (SRS-A) -- the latter responsible for bronchial constriction in asthma.

Histamine is considered responsible for much of the swelling and itching characteristic of hay fever and other allergies. Dr. Allen P. Kaplan, AADC director in the NIH Clinical Center, Bethesda, has shown that histamine can selectively attract eosinophils to the site of allergic reactions in tissue. This attraction depends on the concentration of histamine, that is, the cells will move from an area of low histamine content to one of a higher level. Large doses of histamine, however, were found to inhibit eosinophil migration by immobilizing the cells and keeping them at the site of the allergic reaction. He has demonstrated that histamine is the critical mediator released into the circulation when patients with cold-induced hives are challenged. He also has correlated this release of histamine with the swelling and hypotension characteristic of this disease. Dr. Kaplan is presently investigating the various functions of histamine as well as the role of the eosinophil in allergic reactions.

Another mediator even more potent than histamine in causing tissue swelling is bradykinin. This substance is a byproduct of the early chemical reactions which simultaneously start and dissolve blood clots. Dr. Kaplan has been studying

the pathway by which bradykinin is produced in patients with asthma, chronic hives, and angioedema (chronic swelling). He has found a new high molecular weight form of kininogen -- the precursor blood protein from which bradykinin is derived -- which comprises only about 15% of the total amount of kininogen in the blood. This kininogen was found to be absolutely essential to the activation of the first protein component in the series of chemical reactions of clot formation and dissolution. Thus it represents a new clotting factor as well as the substance from which the chemical mediator bradykinin is formed. This finding is not only important to our understanding of the formation of bradykinin but may help us to determine the role that blood clotting plays in many inflammatory diseases including allergies, arthritis, and kidney disease.

Development of Allergy. Basic research studies such as those investigating IgE and chemical mediators will further the understanding of how allergic and non-allergic individuals differ. Scientists still do not know whether a person's genetic makeup alone determines his susceptibility to allergies at some point in his life or whether some other event actually triggers allergic sensitization.

Allergy Center Director Dr. Oscar L. Frick, University of California, San Francisco, is attempting to answer this question by following a group of infants for the first five years of their lives. Coming from families in which both parents, as well as one or more siblings or grandparents, have allergies, these children are thought to be at high risk of developing allergies early in life. In fact, after two years of study, five of seven children followed have indeed de-developed eczema and/or asthma. Interestingly, however, the onset of allergic symptoms in all children occurred after an upper respiratory infection. Tests which were negative for IgE antibodies prior to the infection becamse positive for one or more allergens (house dust mites and foods) within weeks after the infection.

If external events which initiate allergic sensitization can be identified, allergy experts might be able to prevent the development of allergy in individuals known to be genetically predisposed. This could be accomplished by avoiding exposure to such environmental factors or by taking immediate precautionary measures should exposure occur.

Asthma. Asthma is a noncontagious disease of the large and small bronchial tubes which affects an estimated 9 million Americans. Normally, the airways offer little resistance to the flow of air. During an asthmatic attack, however, 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 produces the wheezing sounds that are typical of asthma.

For years, asthmatics have been classified according to the factors causing their attacks. In extrinsic asthma, outside factors, mainly allergies, provoke the attack whereas in intrinsic asthma, no external factors can be identified. Most adult asthmatics fall into the intrinsic category.

However, it has been recognized recently that the asthmatic population is too heterogeneous to be so narrowly classified. Dr. Richard S. Farr, director of the AADC at National Jewish Hospital and Research Center in Denver, has devised a new scheme to characterize asthmatics based on a highly accurate computerized collection of data on individual patients. This system now enables physicians to have daily access to such reports as the results of patients' morning and evening breathing tests, their daily medicine requirements, with special emphasis on their steroid dosage and their special medications "as needed" to control asthmatic attacks that occur despite their regular medical treatment. These last 2 parameters, along with the data on as asthmatic's pulmonary function, have been shown to be the most sensitive indicators of a given patient's progress. Thus,

asthmatics may now be more accurately classified and treated on an individualized basis.

This computer data base of the daily condition of a large number of asthmatics has enabled Dr. Farr to correlate increases in the number of attacks in these patients with rises in the levels of smog in Denver. Although scientists have suspected for some time that high carbon dioxide levels adversely affect asthmatics, the rematching of these data with the smog levels monitored on the campus of the National Jewish Hospital has provided statistical evidence of this relationship. The Environmental Protection Agency is already consulting with Dr. Farr on the use of his valuable data for further studies.

Treatment of Asthma. An important addition to the list of drugs effective in the treatment of asthma may be a familiar pharmacologic agent, atropine, administered in a new way. This drug acts by blocking a chemical involved in the contractions of smooth muscles. It is possible that atropine administered in an aerosol form, would aid an asthmatic by acting directly upon the smooth muscles in the lung area which contract and close down the passageways of the bronchioli in these patients when they are exposed to allergens, air pollution, or other respiratory irritants.

Dr. Elliot Middleton, AADC director at the National Asthma Center in Denver, used atropine to treat chronically ill children whose asthma was resistant to the maximum amounts of other drugs. Atropine produced excellent dilation of the children's bronchial tubes. The results of this study not only provide physicians with a new modality to treat asthma but also add an important new dimension to asthma research.

Treatment of asthma in pregnant women poses a special problem. In pregnant animals, steroids -- often the only agents that will effectively control severe asthma -- have been known to cause an increased incidence of abortions, placental insufficiency, and congenital malformations in offspring.

Dr. Roy Patterson, AADC director at Northwestern Medical School in Chicago, in collaboration with a scientist at the University of Washington, Seattle, studied last year the record of a group of pregnant women with asthma who were treated with steroids. The scientists found that the risk to the fetus of insufficient oxygen associated with the mother's severe asthma is a greater potential hazard than the careful use of corticosteroids. In Dr. Patterson's study, there were no maternal, fetal, or neonatal deaths nor any increase in toxemia, uterine hemorrhage, or congenital malformations. The only unusual finding was a slightly higher number of premature births. The results of this study resolve the previously conflicting data on steroid treatment of pregnant women with asthma and favor control of their symptoms by defined dosages and medication schedules.

Food Allergy. Millions of Americans at some time in their lives have had hives, the most common cause of which is an allergic reaction to foods. However, in some patients, food allergies may cause eczema, vomiting, diarrhea, asthma, rhinitis, migraine headache, angioedema, and serious shock or even death.

Unlike several other types of allergic reactions, food allergies do not respond to treatment with injections of food extracts. The only recourse is avoidance of foods to which one knows he is allergic. Therefore, Dr. Arthur Malley, an NIAID grantee at DRR's Oregon Regional Primate Research Center, Beaverton, is investigating potential ways to improve immunotherapy for food allergy, in this case, caused by a common allergen, the green pea.

Based on his earlier, but continuing work with allergy to timothy grass pollen, Dr. Malley separated an extract of green peas into four fractions. Tests in rabbits and the laboratory revealed that one of these, the albumin fraction, appeared to be responsible for causing allergic reactions. Another fraction, however, the pea dialysate fraction, due to its inhibition of certain experimental

reactions, may be a key to improved therapy because it appears to be capable of interfering with allergic reactions to peas. Further studies suggest that the albumin fraction may represent a common allergenic fraction among members of the legume family, and the dialysate fraction may similarly be able to inhibit reactions to various legumes. Preliminary reports, using the dialysate fraction as a model for studying patients sensitive to peas, suggest its possible efficacy in immunotherapy.

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 specifically sensitive to them can lead to a serious drop in blood pressure, shock, and possibly death. Annually in this country, as many as 50 reported fatalities follow such stings. Undoubtedly, many more deaths occur but may be mistakenly diagnosed as heart attacks, stroke, or convulsions.

For many years, physicians have been treating people allergic to insect stings 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.

However, because exposure is usually not to the whole insect, but rather to the venom, scientists at two NIAID Asthma and Allergic Disease Centers are studying the usefulness of skin testing and immunotherapy with venom alone. Dr. Philip S. Norman at Johns Hopkins University and Dr. Carl E. Arbesman at the State University of New York (SUNY) in Buffalo, along with their associates, have both shown, through tests in the laboratory and in allergic individuals, that the use of pure venom is superior to whole body extracts for diagnosing and treating these reactions. Both groups found that total levels of immunoglobulin G (IgG), the antibody believed to be responsible for blocking beneficially the reaction between IgE and a particular allergen, were significantly stimulated by venom extracts. The SUNY study showed that IgG was not increased by whole body preparations. Following treatment with pure venom, patients in the Johns Hopkins University project have been restung under controlled hospital conditions and none has experienced a systemic reaction, as each had prior to treatment.

As anyone who has ever been stung knows, bee venom contains material which is inflammatory to body cells. Therefore, scientists working under Dr. Arbesman have developed a purified form of bee venom for use in immunotherapy which might be less toxic but would retain its ability to stimulate antibody production. A similar product, known as "allergoid," is under evaluation at Johns Hopkins University for treating allergic rhinitis, or "hay fever."

Using the method worked out for producing the allergoids, SUNY researchers treated honeybee venom with formaldehyde to produce a "venomoid." Tests in the laboratory and in rabbits suggest that this material is indeed less toxic than venom, but is able to combine with IgE antibodies almost as well. In rabbits it seems also to stimulate the antibody production in a manner similar to venom. Studies are continuing to improve "venomoid" for further research.

Allergists in Florida have found that the South American fire ant--introduced into this country in the early 1900's--is an underrated cause of insect allergy. This ant has invaded more than 150 million acres of 13 southern states. University of Florida, Gainesville, investigators Drs. Robert B. Rhoades and Heinz J. Wittig, partially supported by NIAID in cooperation with a group of practicing allergists, studied people who had experienced systemic (whole body) reactions after a fire ant bite. These reactions usually consisted of hives and/or angioedema (giant hives), but sometimes also difficulty in breathing, tightness of the chest, wheezing, sweating, nausea, unconsciousness, or itching.

After treating these people with injections of fire ant extract, the scientists concluded that the threat of systemic reactions appeared to be successfully

reduced by such immunotherapy. However, the availability of this treatment and the severe life-threatening nature of fire ant allergy are apparently being overlooked not only by patients, but also by their physicians. They believe that the common practice of equating any ant sensitivity with that of fire ant sensitivity poses a hazard to patients. The scientists recommend that, at least at present, people with suspected ant allergy should be tested and treated for specific ant sensitivities.

These researchers hope to provide a more rational approach to the treatment of fire ant allergy by resolving such major problems as the chemical nature of the fire ant venom.

Organ Transplantation

Over the past 20 years, significant progress has been made in the field of transplantation. Laboratory research has enabled surgeons to apply experimental findings to animal models, and finally to humans. Although this transition had an initially high mortality rate, the number of long-term survivors of kidney, heart, and bone marrow transplants has dramatically increased. Immunology must now solve the remaining problems, such as graft rejection, which prevent transplantation from being a routine procedure.

To achieve this goal, scientists are trying to learn how to manipulate the immune response of a recipient so that he will accept the "foreign" graft but retain his ability to fight off disease-producing organisms. This delicate balance requires a more complete understanding of the major histocompatibility complex--the group of inherited genes that regulate an individual's immune response--and of the types of cells and mechanisms involved in organ rejection.

Donor Selection. Since not enough kidneys are donated to meet today's needs, every organ must be given the best possible chance for survival, that is, it must be transplanted into the most closely matched recipient. It has been shown that more than 60% of transplanted kidneys that fail do so because of genetic differences between the donor and recipient. These genetic differences can be recognized by serologic (blood) tests which identify specific HLA antigens. These serologically-defined (SD) HLA antigens are substances which are found on the surface of certain cells, mainly white blood cells called lymphocytes.

Each individual possesses four of these antigens, two from each parent. Consequently, identical twins who have the same genetic markers are the ideal donor-recipient combination. A brother or sister offers the next best hope of genetic compatibility since there is a one in four chance that they inherited the same antigens from their parents. However, the source of most transplanted organs today are cadavers, totally unrelated to the recipient. Thus, the importance of precise typing techniques for matching donors and recipients is obvious.

Today, there are 4 known loci of the HLA system with 51 different antigens. (More probably exist but have not yet been identified.) NIAID's Transplantation and Immunology Branch (TIB), under Dr. Donald Kayhoe, is the world's chief source of reagents that identify these antigens. Currently, the NIAID Serum Bank is stocked with approximately 1600 different sera. Through a system of contracts, TIB collects, analyzes, and distributes these reagents to approximately 400 laboratories in this country and abroad. This program thus makes possible the matching of donors and recipients for organ transplants and for white cell and platelet transfusions. The sera are also used in studies of the relationship of HLA antigens to disease susceptibility.

Matching of prospective donors and recipients of solid organ and bone marrow transplants is facilitated by a standardized typing tray, available through the TIB. Each tray is preloaded with 68 reliable antisera which recognize 37 different antigens. These trays can be frozen and shipped anywhere in the United

States. In 1975, over 25,000 trays were distributed. Since 95% of all U.S. kidney transplant hospitals use NIH trays to type for transplantation, the value of this service cannot be overemphasized.

It has been recognized for some time that the SD antigens of the HLA system do not represent the entire story, since another technique, known as MLC, clearly recognized other genetic differences. However, the MLC test requires a time period longer than a cadaver kidney can survive.

This past year, Dr. Fritz Bach, a NIAID grantee at the University of Wisconsin, and his coworkers have developed a new test which identifies these specific lymphocyte-defined (LD) antigens in a shorter time. A panel of test cells is prepared by "primimg" them through incubation with cells known to differ by only one specificity. The primed test cells can be stored or frozen until needed to type a recipient and donor for transplant. When an individual's cells are incubated with these primed cells, the response--rapid multiplication--occurs within 24 hours, instead of the usual 4 to 5 days. This shortened time requirement may lead to better matching of patients and cadaver kidneys.

Preformed Antibodies. In addition to selecting a donor who is genetically compatible, scientists have realized that they must be certain that a recipient does not have any preformed antibodies against the donor's cells. These antibodies may have been formed when the recipient was preimmunized to the histocompatibility antigens by a previous transplant, blood transfusions, pregnancies, or possibly, some types of infection. Such antibodies can destroy the transplanted cells.

Techniques to predict the presence and type of preformed antibodies have had several drawbacks, limiting their usefulness. Dr. James Lightbody, a NIAID grantee at Wayne State University, has recently developed a more sensitive assay for these antibodies. He has used flourescent dye to determine the destruction of cells coated with preformed antibody by killer T cells--a special kind of lymphocyte. Since cells not coated with antibody will not be killed by the T cells, this test should enable doctors to determine whether or not an individual is a suitable recipient for a particular organ.

Histocompatibility Systems of Other Species. In order to understand the genetics of the human histocompatibility system, scientists have found it necessary to study similar systems in species such as the mouse. To assist these studies, NIAID's Transplantation and Immunology Branch has contracted with Dr. Marianna Cherry of Jackson Laboratories, Bar Harbor, Maine, to produce, store, and distribute to qualified investigators the mouse H-2 alloantisera, analogous to the human HLA typing sera. More than 200 scientists use these mouse antisera for basic research in the genetics of the immune response, graft rejection, tissue compatibility, and tumor formation.

In addition to these antigens of the major histocompatibility locus, the mouse also has antigens determined by other genes, known as the non H-2, which are present on different chromosomes. Although the individual antigens of the non H-2 genes are weak, their combined ability to elicit an immune response appears to be as great as that of the H-2 antigens. Dr. Ralph Graff, a NIAID grantee at Jewish Hospital of St. Louis, Missouri, has found that certain non H-2 genes can have many alleles, that is, alternate forms of the genes that determine different antigens. The existence of these many possible antigens means that it would be almost impossible to find a perfectly matched donor in the random mouse population. Dr. Graff is currently evaluating the effects on graft survival of partial matching of these different antigens.

A parallel situation to the mouse non H-2 loci has been found in dogs by Dr. Felix Rapaport, a NIAID grantee at New York University Medical Center. He has clearly demonstrated the existence of the DhR system as distinct from the DL-A major histocompatibility locus in dogs. The factors produced by DhR cause prompt

rejection of bone marrow and kidney transplants in DL-A identical dogs. These systems may shed light on the corresponding human situation where recipients of bone marrow transplants from HLA identical siblings may nevertheless develop fatal complications.

Immunosuppression. Since genetically identical matches of a donor and recipient are difficult to achieve, scientists have had to rely on various techniques to manipulate the patient's immune responses. One commonly employed method is to treat the recipient with drugs, such as corticosteroids, which suppress his ability to mount an immune response not only to his graft, but unfortunately, to disease-producing organisms as well. It is the goal of scientists to understand the mechanism of action of these drugs so that eventually they can be used to block only the immune response to the graft.

Research towards this goal is being conducted by NIAID's Laboratory of Clinical Investigation. Dr. Anthony Fauci has clearly demonstrated that corticosteroids--which were previously thought to act by destroying normal human lymphocytes--cause a selective and transient decrease in circulating lymphocytes and monocytes. This depletion of certain subpopulations of cells is caused by the drug-induced redistribution of these cells from the circulating blood to other body sites. In addition, the scientists found that corticosteroids cause a selective depression of certain functions of lymphocytes.

Another form of immunosuppression consists of administration of antisera directed against T lymphocytes--the particular type of white cell that has been implicated in graft rejection. NIAID's Transplantation and Immunology Branch has developed through interagency agreement with Dr. Kenneth Sell of the National Naval Medical Center, a rabbit anti-human thymocyte globulin (RAHTG) which has been found effective in prolonging skin and kidney grafts in subhuman primates. In a double blind study, Dr. Oscar Salvatiera of the University of California at San Francisco is studying approximately 100 kidney transplant recipients, 50 of whom have received this material. Through a contract with TIB, Dr. Salvatiera is providing the clinical data on these patients, which should elucidate the role that RAHTG plays in preventing graft rejection in humans.

Tolerance. Scientists are searching for methods of producing organ acceptance without interfering with the recipient's immunologic defenses. Animal studies have shown that immune responses to a transplant will be suppressed if the prospective recipient is exposed to donor cells during fetal life. In NIAID grant-supported work, Dr. Rapaport has found that this early period of adaptability can be duplicated in adult dogs by total body irradiation. Using specially bred animals, Dr. Rapaport found that transplantation of bone marrow from prospective donors, identical for major histocompatibility characteristics, into irradiated recipients resulted in tolerance of the recipient to subsequent transplants of skin, kidney, heart, lung, liver and pancreas from the same marrow donor. Current studies suggest that this form of tolerance may also be induced to "third party" donor organs, if the "third party" is genetically compatible with the marrow donor.

Other tolerance studies are being carried out at the University of Texas Health Science Center by NIAID contractor and grantee, Drs. Rupert Billingham, J.W. Streilein and co-workers. They have found that induction of tolerance to weak transplantation antigens is influenced by the presence of an intact spleen, thus identifying the difficulty of inducing tolerance in animals whose spleens had been removed. Furthermore, in tolerant animals with spleens, the transfer of cells sensitized against antigens on the tolerated graft did not abolish the tolerance. In contrast, sensitized cells did break the tolerance in splenectomized animals. These studies indicate that the spleen may be able to blunt T-cell mediated immune reactions, such as graft rejection.

Genetic Control of the Immune Response. As has been explained, an important function of the major histocompatibility complex is the genetic encoding of

specific markers, or antigens, on tissue surfaces. If these markers on a graft differ from those of a recipient, then the immune response will go into action. However, scientists do not believe that graft rejection is the sole function of this genetic complex.

Indeed, it has now been found that the major histocompatibility complex determines not only the structure of transplantation antigens but also the body's ability to make strong or weak immune responses to a wide variety of antigens, presumably all we will ever encounter. This ability is controlled by a set of genes known as the immune response (Ir) genes. In the mouse and the guinea pig, these immune response genes are found in the I region of the MHC. Therefore, cell membrane proteins whose structure is controlled by this region are known as the I region associated (Ia) antigens. These Ia antigens are found predominantly on the surface of immunologically competent cells--lymphocytes and macrophages. Their functional role in the immune response must now be determined.

Dr. Hugh McDevitt, a NIAID grantee at Stanford University School of Medicine, and co-workers have studied the effect of the Ia antigens upon antigen recognition by T cells (thymus dependent lymphocytes) and B cells (thymus independent lymphocytes) in the mouse. B cells, whose function is antibody production, appear to carry Ia antigens on their surface. Furthermore, they found that the T cells involved in regulating the B cell response--either by initiating it (helper T cells) or by suppressing it (suppressor T cells)--also appear to carry Ia antigens. This is further evidence that the Ia antigens play a central role in regulating the immune response. It may be that the Ia antigens are the gene products which mediate the Ir gene effects. Isolation and chemical characterization of the Ia antigens should enable scientists to better understand this new antigen recognition system and possibly to manipulate it in a manner beneficial to an individual patient.

Drs. Benjamin Schwartz, Ethan Shevach, and William Paul of NIAID's Laboratory of Immunology are studying the structure of Ia antigens in the guinea pig. They have found these antigens on molecules separate from those carrying the histocompatibility antigens. These scientists have chemically characterized the Ia antigens, determined their size, and demonstrated that they each consist of two distinct polypeptide chains. Further studies of their chemical nature, heterogeneity, and specificity are underway.

Cellular Aspects of the Immune Response. Since cellular immune responses, as mediated by T cells, appear to be crucial in graft rejection, Dr. Alan Rosenthal of NIAID's Laboratory of Clinical Investigation is attempting to define how the T cells recognize the graft antigens as foreign. By immunizing guinea pigs with simple but clinically important substances, such as insulin, Drs. Rosenthal, Barcinski and Rosenwasser have been able to study T cell immune responses. They have found that the T cell is not capable of direct interaction with soluble protein antigens. Rather, another type of cell, the macrophage, must first interact with the antigen, process it, and present it to the T cell.

In addition, NIAID's Drs. Shevach and Rosenthal have shown that macrophages which have been specifically exposed to antigens, responsiveness to which is controlled by specific Ir genes, fail to stimulate an immune response by primed lymphocytes unless both types of cells possess identical Ir genes and Ia antigens. This suggests that the Ir genes--or genes closely linked to them--play an essential role in the specific function of macrophages.

In a recent study, Drs. Rosenthal, J. Thomas Blake, and Peter Lipsky investigated the action of the fungal product, cytochalasin B, which inhibits in vitro the recognition of antigen by T cells. They have found that this chemical does not interfere with the uptake of antigen by the macrophage but rather inhibits the development of physical interactions between the macrophage and T cell. A more complete understanding of this blocking of cell cooperation may eventually lead to a more specific means than total immunosuppression for blocking immune

responses against a graft.

Recent work has established that T lymphocytes may play a role in regulating antibody production. Under certain conditions, activated T lymphocytes may specifically inhibit (or suppress) the antibody response to a given antigen. Drs. Patrice Debré, Baruj Benacerraf--a NIAID grantee at Harvard Medical School--and co-workers have shown that specific genes wihtin the mouse MHC may control the "suppressor" activities of T lymphocytes. This study provides insights into additional ways in which the MHC may regulate specific immune responses. It suggests an important mechanism through which association of HLA antigens and diseases in humans may be mediated.

HLA Antigens and Disease. The general importance of HLA antigens is emphasized by recent findings that several different diseases occur in statistically higher frequencies in individuals with specific HLA types. These conditions include ankylosing spondylitis--an arthritis-like disease of the spine--multiple sclerosis, and gluten sensitive enteropathy--an intolerance to wheat and rye proteins. The presence in humans of immune response genes linked to a particular HLA or MLR type may be one reason for this association.

Using a computer data bank at Stanford University, Dr. Hugh McDevitt, a NIAID grantee, is analyzing clinical data on patients to identify any relationship between the major histocompatibility system and susceptibility to a variety of diseases. So far the antigen HLA-B27 has been found to occur frequently in patients with ankylosing spondylitis (AS). Dr. McDevitt has found that 20% of "normal" individuals with HLA-B27 have definite, though mild or subclinical, cases of AS. This disproves earlier, much lower estimates and should have a major impact on our understanding of the epidemiology and genetics of the disease.

Dr. McDevitt has also found a relationship between disease states and the antigens recognized by the mixed leucocyte test, now known as the LD antigens. He found that patients with Graves Disease--a disease of the thyroid gland in which excessive amounts of hormones are secreted--show a marked increase in incidence of of HLA-D3, an antigen that is found in association with the SD antigen, HLA-B8. Patients with Graves Disease were found to have an increased incidence of both antigens. Use of a panel of MLC typing cells in studies of a wide variety of diseases such as rheumatoid arthritis, diabetes, and Wegener's Granulomatosis, may provide a new approach to understanding how and why some people develop these conditions.

Currently, 98 U.S. labs are studying the relationship between HLA antigens and diseases. These studies would be impossible without the typing reagents made available by NIAID's Transplantation and Immunology Branch.

Kidney Transplantation. A successful kidney transplant can "cure" chronic kidney disease. Kidney dialysis--in which a patient's blood is mechanically purified--keeps the patient with kidney failure alive but the quality of his life is rather poor. He must spend 6 to 8 hours a day, two to three times a week, connected to the dialysis machine. This machine dependence consumes a major part of his time, confines him to one locale, and can affect him psychologically. Furthermore, dialysis is often a downhill road since the patient continues to be ill, and it is usually only a matter of time until he has no suitable veins with which to be connected to the machine. An analysis of kidney transplant patients at the Medical College of Virginia by NIAID grantee Dr. Hyung Lee, showed that 50% of his patients who received transplants were still alive after 10 years. This 10-year survival is a great deal better than for those on dialysis.

Thus, the ideal situation for a person with kidney failure is to be kept alive by dialysis until a suitable donor is found for a kidney transplant. Should the transplant fail, dialysis can again keep the patient alive until there is another opportunity for a transplant.

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Most transplanted kidneys that fail do so because of genetic differences that cause rejection. HLA typing to detect these genetic differences has been recognized as very important to graft survival when the donor is a living relative of the recipient. However, the value of HLA matching in transplants involving cadaver kidneys--the most common source of today's transplants--has not been established. NIAID's Transplantation and Immunology Branch is therefore supporting a large scale evaluation of HLA typing in cadaver kidney transplants.

This evaluation includes contracts with 17 regional centers involving 20 tissue typing laboratories and 40 transplant hospitals to collect and submit data on 2,500 cases of kidney transplants, 1,200 of which have already been entered. Kidney and patient survivals will be statistically analyzed through a contract with the Naval Medical Research Institute in Bethesda. Since data are being collected on many clinical features and laboratory studies, there is a potential for receiving valuable information about factors other than histocompatibility in kidney transplantation.

For example, it has already been learned that most men in the study are between the ages of 20 and 49, while most women are between the ages of 10 and 39. Most failures of the transplanted kidney were due to acute or chronic rejection. Glomerulonephritis--an inflammation of the clusters of blood vessels in the kidney due to unknown causes--is the primary disease causing kidney failure and necessitating a transplant.

Drs. Anthony Fauci, James Balow, and Sheldon Wolff of NIAID's Laboratory of Clinical Investigation, have shown that kidney transplant can be of tremendous value in patients with Wegener's Granulomatosis. This relatively rare disease is characterized by granuloma formation--tumor-like masses of tissue--and inflammation of small blood vessels, particularly in the upper respiratory tract, the lungs, and the kidneys. Until recently, it has been a universally fatal disease. Drs. Fauci and Wolff have been able to achieve remission of the disease with immunosuppressive drugs, but some patients still have developed end-stage renal failure, particularly when immunotherapy was instituted late in the course of the disease.

However, in collaboration with surgeons in Massachusetts and Rhode Island, they have now successfully transplanted kidneys into 2 patients with Wegener's Granulomatosis in whom they had induced remission. These patients have now survived for more than 2 years, thus offering new hope to patients with a previously fatal disease.

Methods of prolonging graft survival are being investigated by Dr. Richard Wilson, a NIAID grantee at the Harvard Medical School. He first isolated the antigen-binding fragments of the antibody molecules specifically directed against a monkey donor kidney. These fragments were then circulated through the donor kidneys for an hour prior to their transplantation into immunosuppressed monkeys who had been sensitized to the donor. The monkeys who received the fragment-treated kidneys achieved normal kidney function, whereas monkeys, receiving untreated kidneys quickly rejected them.

Dr. Wilson is now preparing human fragments of antibodies developed by patients on dialysis and has also developed a test to measure the fragment's blocking capability in human serum. Continuation of these studies will facilitate the use of these fragments to interfere with the antibody-mediated destruction of grafts in humans.

Studies by Dr. Lee at Medical College of Virginia have also shown the importance of the T lymphocyte in graft rejection. Dr. Lee and his associates found that patients who rejected their kidney transplants had a high level of reactive T cells whereas those patients whose transplanted kidneys had already survived for more than 10 years had a specific defect in their ability to generate killer T cells. Thus, a major reason for the long term survival of mismatched cadaver

kidneys seems to be a blocking of development of T cells which can destroy the graft. Dr. Lee is currently studying the mechanism involved in blockage of this T cell response.

Cytomegalovirus (CMV)--a member of the herpes family of viruses characterized by recurrent periods of latency during which time the virus hides in the body--occurs frequently in kidney transplant recipients. Scientists are studying this virus infection to see if it has an effect upon the graft's survival. Dr. Monto Ho and a team at the University of Pittsburgh--grantees of NIAID and the National Heart and Lung Institute--have produced evidence that the transplanted kidney itself is the source of CMV infection.

Dr. Richard Freeman, Dr. Robert Betts, a grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), and co-workers at the University of Rochester have also found evidence that the transplanted kidney is the source of CMV infection and that immunosuppressive therapy of transplant recipients reactivates the virus. They have also shown that there is a definitive correlation between the presence of CMV infection and failure of the transplanted kidney.

Dr. John Najarian, a NIAMDD grantee, and co-workers at the University of Minnesota have found two different types of responses to CMV infections in kidney transplant patients. In the immunocompetent patient, CMV is associated with kidney graft rejection, a prompt antibody response to the virus and recovery from the infection. However, the severely immunosuppressed patient cannot make antibody and does not reject his graft. In addition, this type of patient may be further immunosuppressed by the viral infection, making him susceptible to other infections which prove fatal.

Bone Marrow Transplantation. Supported by NIAID and the National Cancer Institute, Dr. E. Donnall Thomas and other investigators at the University of Washington have become the leading transplanters of bone marrow in the world. In 1975, they performed 64 marrow transplants for patients with acute leukemia, or aplastic anemia--a disorder in which the bone marrow fails to produce blood cells. Thirty-five of these patients are still alive. The longest aplastic anemia survivor is now 4 years post transplant. The longest acute leukemia survivor who received a transplant from a twin has now been free of his disease for 5 years, thus demonstrating a "5 year cure" by bone marrow grafting. Another leukemia patient, who no longer responded to chemotherapy, received a bone marrow graft from his sister. His bone marrow is still female and after 5 years, he is still free of his disease.

These two leukemia patients with long-term cures indicate the feasibility of intensive therapy designed to destroy both normal and abnormal marrow cells followed by a marrow transplant to restore normal marrow function. There are, however, many problems to be solved before this treatment can help all who need it.

One of the most severe problems in bone marrow transplantation is the development of graft-versus-host disease (GVH) in the recipient. In GVH, instead of the recipient rejecting the graft, the immunologically deficient patient is rejected by the graft, usually with a fatal outcome. Progress against GVH should be facilitated by the characterization of subpopulations of lymphoid cells in human bone marrow. Dr. Anthony Fauci of NIAID's Laboratory of Clinical Investigation, using a new method which he developed, has separated purified lymphoid cells and found that the human bone marrow contains approximately 20% B cells, 70% lymphoid cells without detectable markers by which they can be characterized, and 10% T cells with identical or similar characteristics of mature T cells. This finding of "mature" T cells in the marrow itself most likely accounts for T-cell dependent GVH reactions seen so often in bone marrow transplants.

National Heart and Lung Institute

Transplantation Biology. The recipient of an organ or tissue transplant may require transfusions in conjunction with the transplantation procedure. Unfortunately, such transfusions may also introduce histocompatibility antigens that can contribute to rejection of the graft.

National Heart and Lung Institute-supported research indicates that, for the transplant recipient whose primary blood replacement problem is anemia, removal of white cells and platelets (by centrifugation) from blood prior to transfusion reduces the rejection threat. Whole blood that has been frozen and then thawed before transfusion appears to give even better results than does leukocyte-poor blood.

The Institute also supports research concerned with the development of techniques and devices for the preservation and storage of isolated organs for future use in transplantation and is investigating the feasibility of employing the evolving system of regional blood centers as resources for tissue typing and for organ and tissue procurement, preservation, and distribution.

Heart Transplantation. The wave of enthusiasm for heart transplantation that followed hard upon the first successful operation in 1967 diminished considerably during subsequent years. But substantial progress continues to be made in those centers with the facilities, staff, and expertise to cope with immunological and related problems that almost inevitably develop during the post-operative period.

The largest series of heart transplants, and one of the most successful, is that of Dr. Norman Shumway and colleagues at Stanford. As of August 1, 1975, this group had performed 90 heart transplants. Thirty-two recipients were still alive, the longest survivor having gone for 5-2/3 years. For the 53 patients who made it through the critical first three post-operative months, the survival rate was 76-percent after one year and 59-percent after three years. Forty-eight of these were restored to normal activity status by the procedure and many resumed their previous occupations.

The percentage of transplant recipients surviving for a year or more has continued to increase, thanks largely to improved techniques for very early detection of rejection episodes and for monitoring the effects of immunosuppressive therapy. Rejection episodes remain a recurrent problem among long-term survivors, but are no longer a major cause of death. The leading cause of death in this group is infections, resistance to which is inevitably lowered by the immunosuppressive therapy employed to prevent or control rejection episodes.

The Stanford scientists feel that clinical research on heart transplantation should continue, for, in skilled hands, the procedure may well provide additional years of near-normal life to patients otherwise doomed to a bed-ridden existence and a future life expectancy of 6 months or less.

Lung Transplantation. This procedure has been attempted from time to time in patients moribund from far-advanced lung disease. But the results have been so poor (longest survival: 10 months; usual survival: less than 10 days) that there seems little justification for the operation until some of the truly formidable problems have been overcome. These problems continue to be studied in the laboratory and in experimental animals.

National Eye Institute

Cornea Preservation. During the past year new methods have been developed which promise to extend the benefits of corneal transplantation by improving the quality of donor tissue and reducing the risk of graft failure. Of the nearly 3,000 corneal transplants performed each year in the United States, between 75 and 85 percent are successful. In the remaining 15 to 25 percent, one of the main

problems associated with graft failure is loss of tissue transparency following the operation. Often this is caused by an inability to preserve the cornea's endothelial cells from the time the tissue is obtained until it is used for transplantation. This layer of cells functions as a biologic pump, removing water from the cornea and, thus, helping to maintain its transparency. Loss of these cells, not always apparent prior to transplantation, causes the grafted tissue to swell and become opaque.

Investigators at the University of Florida in Gainesville developed a simple, easy-to-prepare solution for storing donor corneas that significantly extends the survival time of healthy tissue, including the vital endothelial cells. The solution, which the investigators call the M-K medium, reduces the risk of postoperative tissue failure and extends the period of preservation for a healthy cornea from the traditional 48 hours to one week. It is now being used by eye banks across the country to preserve donor corneas for transplantation. In addition, because the M-K medium preserves endothelial cells so successfully, some medical centers are also using the solution to prepare fresh tissue intended for immediate transplantation. Additional work is underway, and the developers of the medium believe their technique may be applied to the development of new means of storing other body organs and tissues to be used in transplantation.

A second team of investigators at the University of Florida is working on another, even more simplified method for storage and preservation of donor corneas. Their technique makes use of a salt solution fortified with nutrients to maintain the cornea. This second technique may extend the preservation period of donor corneas to two weeks. Both preservation methods have significant potential for increasing the supply of readily-available healthy corneas, reducing the risk of graft failure, and making it possible to schedule surgery under the most favorable conditions for both the patient and the operating team.

Donor Selection. Because of the absence of blood vessels in the cornea, matching of antigens between donor and recipient is less crucial in corneal transplantation than in other organ or tissue transplant operations. Immune graft rejection occurs in only 5 to 10 percent of all corneal transplantations. However, when, in the course of certain diseases, the cornea becomes densely vascularized, the graft rejection rate increases substantially; as many as 25 to 60 percent of transplants involving a vascularized cornea are not successful. Furthermore, as in kidney transplants, patients receiving a donor cornea are at even greater risk of experiencing graft rejection if they have been presensitized to HLA antigens following pregnancy, blood transfusion, or a previous corneal transplant.

Precise antigen matching between donor and recipient to prevent graft rejection is difficult because of the complex HLA antigen system, now known to include 51 antigens. To overcome this difficulty, National Eye Institute-supported investigators at Johns Hopkins University and other medical research centers have found that the risk of rejection may be reduced by the simpler process called cross-matching. In this procedure, care is taken to avoid using for transplantation a donor cornea with those antigens to which the recipient is already pre-sensitized. Cross-matching thus eliminated the problem of identifying a donor cornea with the specific antigens carried by each person.

This work may make it possible within the next few years to predict the chances for a successful graft in presensitized patients. It may also extend the benefits of transplantation to patients with vascularized corneas for whom transplantation is now a high-risk procedure.

Protection of Transplanted Corneas. Chemical burns are among the most difficult corneal problems to treat and often result in permanent blindness. Transplants in such cases are seldom, if ever, successful because of the recurrent corneal ulcerations, dryness, and scarred eyelids caused by chemical burns; together, these can damage a new graft and prevent restoration of vision.

Several National Eye Institute-supported investigators have now reported encouraging, although short-term, results in protecting the newly-grafted tissue with a hydrophilic or soft contact lens. The soft lens protects the surface of the cornea, allowing it to grow, and also facilitates healing of the ulcers. It acts as a shield against rough, scarred eyelids and, together with eyedrops, helps keep the eye moist.

Although preliminary, results to date indicate that continued research is warranted. The primary objective is development of an improved therapeutic soft contact lens that can be worn continuously and safely for several years. These efforts may make it possible to achieve long-term, successful corneal transplantation for patients blinded by chemical burns.

CYSTIC FIBROSIS

The clinical picture of the inherited metabolic disorder, cystic fibrosis, is brighter than it has been in years past, though the exact nature of its basic chemical defect still eludes investigators. Even though strides have been made in alleviating the complications of the disease, more specific and effective methods of its treatment, management, and possibly prevention must still be found.

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 possibly, eventual prevention of this disease.

In addition to investigations carried out at its research laboratories and clinics in Bethesda, Md., 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

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health: National Institute of Arthritis, Metabolism, and Digestive Diseases	$2,525,000	$2,499,000	$2,680,000	$2,892,000	$2,788,000
Health Services Administration: Maternal and Child Health/Bureau of Community Health Services.	1/	1/	1/	1/	
Total	$2,525,000	$2,499,000	$2,680,000	$2,892,000	$2,788,000

1/ Obligations not identifiable.

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 progressive, 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 - the leading cause of death in these patients. The lung changes may also restrict pulmonary blood flow, leading to increased blood pressure in the lung, 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 concerning pulmonary 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 microorganisms, 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.

Pseudomonas Vaccine in Cystic Fibrosis

Infection with the bacterium Pseudomonas aeruginosa is found with disturbing frequency in patients with cystic fibrosis, burns, cancer, and cardiopulmonary diseases. Antibiotic treatment of serious infection is often unsuccessful, and mortality has been reported to be as high as 80 percent when there is pulmonary involvement with this organism.

Active immunization of susceptible patients with Pseudomonas vaccine has been advocated as a possible means of preventing or improving the prognosis. A joint study by the National Institute of Arthritis, Metabolism, and Digestive Diseases, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases evaluated a Pseudomonas vaccine in 34 patients: 22 with acute leukemia, and 12 cystic fibrosis patients.

Of the 34 subjects, 32 had an excellent serum antibody response to immunization with the vaccine. The leukemia patients' responses, however, were generally somewhat weaker and lasted a shorter period of time than those of the CF group. While the vaccine elicited adverse reactions in a majority of patients, the leukemia subjects experienced greater toxicity. The better tolerance of the vaccine by the CF patients may perhaps be due to their long-term antigenic exposure to the organism due to colonization of the airways and sputum. The addition of a corticosteroid (anti-inflammatory agent) to the vaccine mitigated the adverse effects of the treatment.

Despite the excellent serum antibody responses that were measured by the investigators Drs. J.E. Pennington, H.Y. Reynolds, R.E. Wood, R.A. Robinson, and A.S. Levine, vaccination did not result in any significant clinical benefit to those vaccinees with cystic fibrosis. This was not surprising since antibody levels in the serum do not usually correlate well with levels in the respiratory tract tissue where these patients' infections usually begin. In addition, the pockets of resistant colonization and infection so characteristic of long-term respiratory tract disease in cystic fibrosis are less accessible to antibodies circulating primarily in the blood. The

investigators concluded that local respiratory tract immunization rather than systemic may be more useful in CF patients.

The investigators also found that white blood cells appear to be the most important protective factor against Pseudomonas infection. The study suggests, therefore, that optimal treatment may well include white blood cell transfusions and antibiotics intercurrently, with the added protection of Pseudomonas antibody induced in the patient by prior prophylactic vaccination. More extensive clinical trials of this vaccine are warranted to further evaluate this method of treatment.

Pneumatosis Intestinalis in Cystic Fibrosis

In clinical studies by NIAMDD scientists at the Clinical Center in Bethesda, a patient with cystic fibrosis was found to have pneumatosis coli (a condition characterized by thin-walled, gas-containing cysts in the colon) associated with rectal prolapse, an outward protrusion of the rectal mucous membrane. Although there are several factors in CF predisposing to pneumatosis, it has been rarely reported in the literature. The investigators believe this to be the first case of its kind in a cystic fibrosis patient.

Pneumatosis intestinalis is a relatively benign condition characterized by the presence of gaseous cysts in the intestinal wall. It is frequently associated with mechanical intestinal obstruction or with chronic lung disease. Since both of these predisposing conditions are common in cystic fibrosis, it is surprising that pneumatosis intestinalis is not reported more often in patients with this disease.

Investigators Drs. Robert E. Wood, Chester J. Herman, Keith W. Johnson, and Paul di Sant' Agnese found the present case most unusual in that it was preceded by rectal prolapse, an uncommon complication of CF at the patient's age of 18. Rectal prolapse has not been reported previously in association with pneumatosis coli.

In the absence of complications, the condition produces vague symptoms, if any, requires no treatment, and may be diagnosed only incidentally. When complications occur, however, they may include life-threatening conditions like intestinal obstruction, knotting of the bowel, perforation, gas or air in the peritoneal cavity, and hemorrhage.

The full history of pneumatosis intestinalis is not known; spontaneous disappearance of lesions has been reported, as has conversely, the persistence of lesions for many years. Since symptoms are non-specific, the investigators suggest that the diagnosis should be considered in patients with cystic fibrosis, or other chronic lung disease, who have vague abdominal complaints.

Presence of Ciliary Inhibitor in Urine

Grantees of the NIAMDD at the University of Texas Medical Branch at Galveston have isolated a factor from the urine of cystic fibrosis patients that inhibits ciliary action normally seen in such biological systems as oyster gills.

Previous research has identified such a factor in the serum and media of cultured cells derived from CF patients. In those studies, the protein

responsible for ciliary inhibition was identified as a polypeptide of small molecular weight associated with the antibody immunoglobulin G (IgG) in serum. Speculation that this polypeptide could also be excreted from the urine of cystic fibrosis genotypes led to this investigation by Drs. Barbara H. Bowman and C. McNeely.

Examination of chromatographic patterns of urine from two CF patients and one normal control subject revealed the presence of three-to-four similar proteins, and one electropositive protein fraction in CF urine which was absent in the normal specimen. When this protein fraction was tested on oyster gills, it was found to inhibit ciliary action. Findings such as these could lead ultimately to a simple, more reliable diagnostic test for cystic fibrosis.

Blood Polyamine Alterations in Cystic Fibrosis

Although the basic defect in cystic fibrosis is unknown, there is general agreement that it is due to an inborn error of metabolism transmitted as an autosomal recessive trait. While research efforts have resulted in effective screening tests for detecting carriers of some other genetic disorders, such as Tay-Sachs disease and sickle cell anemia, a reliable method for detecting carriers of the CF trait has eluded investigators.

Now, recent studies by NIAMDD scientists suggest that blood levels of polyamines (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 blood levels of polyamines might serve to detect CF carriers.

To substantiate this theory, Drs. David W. Lundgren and Paul A. di Sant' Agnese of the National Institute of Arthritis, Metabolism, and Digestive Diseases, and Philip M. Farrell of the National Institute of Child Health and Human Development, evaluated polyamine metabolism in cystic fibrosis by measuring the specific blood polyamine, spermine (Spm), and its precursor, spermidine (Spd), in normal control subjects, CF patients, and asymptomatic carriers of the disease. Male subjects in the latter two groups exhibited a consistent and significant decrease in blood spermine resulting in an elevated Spd/Spm ratio when compared to control males. Polyamine levels in female subjects were more difficult to determine due to fluctuations associated with the menstrual cycle, and further work is required to develop comparable Spd/Spm ratios in women.

Interpretation of these ratios suggests that a factor or factors in cystic fibrosis disturbs the steady state of spermine within the circulation. Tissue concentrations of Spd and Spm vary from organ to organ and their synthesis appears to be increased by various hormones, in cells undergoing rapid regeneration, and in neoplastic tumors. To the best of the scientists' knowledge, decreased spermine levels, however, as described in CF patients and carriers, have never been reported previously in human disease states.

The investigators noted that abnormal polyamine levels represent the first chemical demonstration of an alteration in the level of a low molecular weight metabolite in CF carriers. They propose that CF is associated with a definite disturbance in polyamine metabolism, a factor that may be useful in screening populations for carriers of the cystic fibrosis trait.

Enzyme Activity in the Meconium of CF Infants

NIAMDD grantee Dr. Harry Shwachman and associates of the Harvard Medical School have noted numerous abnormalities in the composition of meconium (mucus-like material in the intestine of the full-term fetus) from newborns with cystic fibrosis. The findings could form the basis for a neonatal CF screening test.

Meconium ileus (intestinal obstruction due to plugging of the intestine with thick oatmeal-like material) represents the earliest manifestation of cystic fibrosis. Among the abnormalities found in this type of meconium are an increase in protein, mucoprotein and glycoprotein content; and a decrease in water and total reducing sugars. The investigators noted that these alterations may hold clues to the etiology and early diagnosis of CF.

In studying the action of lysosomal enzymes (tissue-digesting enzymes) and the disaccharidases (enzymes that split the sugar compounds sucrose, lactose, and maltose) found in the meconium of infants, Dr. Shwachman and his associates found a marked increase in enzymatic activity of all disaccharidases studied in infants with CF. Among the lysosomal enzymes, some increased in activity while others decreased. The activity of the enzyme beta-fucosidase in the meconium of CF infants is particularly noteworthy in that by contrast, no activity was observed in the meconium of healthy infants. This pronounced difference in beta-fucosidase activity could be of special value as an alternative test for screening newborns for cystic fibrosis.

Growth Characteristics and Protein Content of Fibroblasts in CF

Previous research involving tissue culture of fibroblasts (connective tissue cells), lymphocytes and other cells has provided key data for elucidating molecular defects in several inborn errors of metabolism. Similar investigations by NIAMDD scientists utilizing cultured cells are now underway in an effort to discover the underlying defect in cystic fibrosis.

In these studies, growth capability and other basic characteristics of the cultured cells are being established. Proliferation rates were determined by three measures of growth: cell number, DNA levels, and total cellular protein. During rapid growth, cell protein production was also assessed by calculation of the protein/DNA ratio.

On the basis of this research, investigators Drs. Philip M. Farrell, J. Charles Pallavicini, and Marta M. Ulane determined that cystic fibrosis fibroblasts are, in fact, capable of normal growth. The fibroblasts showed, however, evidence of metabolic dysfunction and impaired synthesis of collagen, the main supportive protein of connective tissue. The data also indicate that CF cells exhibit a markedly reduced protein/DNA ratio during the most active growth phase of their tissue culture. Since the DNA content of CF fibroblasts was found to be normal, the change in ratio indicates a decreased cell protein level.

The finding of an apparent reduction in protein synthesis during rapid cell division, coupled with the observation that CF fibroblasts fail to induce normal collagen formation, suggests the possibility of a disturbance in the biochemical regulation of protein synthesis in CF cultured cells. Such an aberration could be, potentially, a genetic marker for cystic fibrosis.

NIAID Effort in Research on Cystic Fibrosis

Although the etiology of cystic fibrosis (CF) is still unknown, it is reasonably certain that the disease is not induced by infections or by the immunologic process. However, respiratory infections are important complications of CF and often shorten the lives of cystic fibrosis patients. The National Institute of Allergy and Infectious Diseases contributes a sizable effort to obtaining new knowledge of the organisms and the body's immune defense mechanisms to them.

For example, the staphylococcal bacteria, which are often responsible for respiratory infections during the early stages of cystic fibrosis, are the subject of 12 grants supported by NIAID. The Institute also supports 63 grants, totaling more than $2.6 million, on investigations into the action of drugs that control bacterial infections and in developing and evaluating new antibiotics. In addition, 40 research grants, totaling $1.8 million, support studies of mechanisms by which bacteria develop drug resistance.

Recent studies by Dr. Julian Davies, University of Wisconsin, have led to the characterization of factors involved in resistance to such antibiotics as streptomycin, kanamycin, gentamycin, tobramycin, neomycin, and butyrosin. Through rapid identification of these resistance factors in clinical specimens, a physician should be able to predict which antibiotics will be effective in treating a patient with cystic fibrosis complicated by a bacterial infection. This should, thereby, reduce the risks of trial and error in patient therapy.

Controlling Respiratory Infections

NIAID is actively supporting research on the development of bacterial and viral vaccines. One such vaccine is expected to protect against at least eight different strains of pneumococcal bacteria. Another is being evaluated for protection against the organisms causing atypical, or mycoplasma pneumonia. Several other vaccines are expected to be effective against respiratory viral diseases. These are all in various stages of development and evaluation.

Largely through the efforts of Dr. Robert Chanock's laboratory at NIAID and Dr. Robert Simpson's contract-supported work at Rutgers University, an attenuated vaccine against respiratory syncytial virus (RSV) is now in early clinical trials. RSV is the most serious of all respiratory viral infections in infants and young children, and is a particular problem in hospital nurseries and children's wards where CF patients are most often found.

Many experts recommend routine use of influenza vaccine in CF patients. NIAID has mounted a major effort to improve vaccines now available and a number of different approaches are being tried. These include use of temperature sensitive mutants in live vaccines and recombinant monospecific inactivated preparations.

Vaccines against parainfluenza viruses and adenoviruses are not as far along but are the subject of other studies by NIAID-supported scientists to limit or prevent infections caused by these respiratory disease agents.

In all, NIAID is supporting 39 grants and contracts totaling over $4 million dealing directly with the development of vaccines against acute respiratory diseases.

NIAID is also heavily committed to investigations in other areas that impinge on the control or prevention of respiratory infections. These include studies of such antiviral substances as Amantadine, interferon, and interferon inducers, and of the immune defense mechanisms involved in localizing and resolving infections.

Rather recently, basic studies on viruses have given birth to a new, highly sophisticated technology known as genetic engineering. This technology may some day make it possible for scientists to repair metabolic defects in CF patients through the introduction of new genetic material into afflicted cells and tissues. The NIAID is supporting research on this technology through both its intramural and extramural programs.

In a spin-off of extramural research on asthma, grantees at Children's Hospital Medical Center, Boston, have extended their studies to a consideration of allergies in cystic fibrosis patients. Drs. Harvey Colton and Robert Zeiger have defined the immunologic basis for asthma resulting from occupational exposure to trypsin (enzyme) dust and are now exploring the possibility that pancreatic enzymes used to treat CF patients may actually precipitate allergic reactions in some of these children.

Pseudomonas Research

Intramurally, Dr. Herbert Y. Reynolds and his co-workers in NIAID's Laboratory of Clinical Investigations have collaborated with NIAMDD investigators in evaluating in cystic fibrosis patients a vaccine against the Pseudomonas aeruginosa.

Although injection with this vaccine appreciably increased antibody titers, the clinical course of the disease in the vaccinees was not improved. Therefore, preliminary attempts were made to immunize the mucous membranes of the nose and throat by aerosol spray. The pseudomonas vaccine was evaluated in a small group of cystic fibrosis patients, and, though the daily application of vaccine for a week was well tolerated, no significant increase in antibody titers in parotid fluid or nasal wash was noted.

Results of these studies have not been encouraging, but the scientists emphasize that these trials have been conducted in teen-age or young adult patients, all of whom had advanced CF as well as pre-existing levels of pseudomonas antibodies. The investigators agree that the benefits of vaccination might be better evaluated if young CF patients could be immunized against pseudomonas before they are initially infected with the organisms. Thus, research directed toward early detection of cystic fibrosis in the newborn is of utmost importance.

Three other aspects of pseudomonas infection in cystic fibrosis have been explored by NIAID scientists:

(1) Intensive study of the pseudomonas microorganism itself has been pursued, principally in collaboration with Dr. Charles Zierdt, Department of Clinical Pathology, NIH Clinical Center. The collaborating scientists have found that the peculiar mucoid P. aeruginosa which colonizes the respiratory tracts of cystic fibrosis patients is a single strain. It can be identified by immunological grouping and by the pattern of bacteriophages (viruses) infecting it. Such a finding narrows the spectrum of potentially infecting

pseudomonas organisms and should make specific immunization and antibiotic therapy easier. Moreover, the organism's unique growth requirements in the altered respiratory secretions of cystic fibrosis patients can now be studied directly.

(2) Opsonizing antibodies that prepare pseudomonas organisms for ingestion by scavenger cells called macrophages have been carefully studied. It has been found that the class of serum antibody known as IgG is most effective in enhancing macrophage efficiency. Thus manipulation of lung-secreted IgG might be a way of improving immunity to pseudmonas organisms in cystic fibrosis patients.

(3) In the process of evaluating patients with chronic obstructive lung disease and with persistent pseudomonas in respiratory secretions, NIAID scientists have found a number of young to middle age adults who have sweating abnormalities--a diagnostic clue for cystic fibrosis. Such patients have apparently far-advanced lung disease but are otherwise in good health and have no evidence of pancreatic malfunction. These patients seem to have a limited form of cystic fibrosis involving the lungs and the sweating system, and to be a part of an evergrowing group of adults with degenerative lung disease.

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 may come.

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 39,000.

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 (NHLI) 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 occur 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 detection 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.

Chronic respiratory diseases constitute an exceedingly complex problem demanding a broadly based, diversified approach to insure that each of the many aspects of the problem will be adequately explored.

Obligations for Emphysema and Chronic Bronchitis

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health:					
National Heart and Lung Institute...	$5,592,000	$8,700,000	$6,188,000	$6,066,000	$5,534,000
Health Services Administration:					
Bureau of Community Health Services..	1,230,000	1/	1/	1/	1/
Bureau of Medical Services.....	1/	1/	200	---	---
Total	6,822,000	8,700,000	6,188,200	6,066,000	5,534,000

1/ Obligations 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 forms in some patients. They are considered together, however, in this report because they usually occur together, and, indeed, it is often impossible to determine which of the two is the more 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 trigger many of the same physiological mechanisms. This phenomenon is reflected in common usage of the collective term "chronic obstructive pulmonary disease," which is largely synonymous with emphysema and chronic bronchitis.

During Fiscal Year 1975, NHLI support of research and training activities in the field of emphysema and chronic bronchitis amounted to $6,188,000. The money was used for research investigations in Institute's laboratories in Bethesda, Md., 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 involved approximately 12 percent of the DLD budget. Additional NHLI research bears only indirectly on the chronic obstructive pulmonary diseases per se, but contributes substantially toward the prevention, diagnosis and treatment of these disorders and their complications, and enhances our understanding of the underlying disease processes. An example is the development of blood oxygenators and ventilatory devices for 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 39,000 Americans; each year, its direct and indirect costs 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.

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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 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 the 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 large numbers of people has been developed which uses a simple, rapid, single-breath test of lung volume and gas exchange. The NHLI has awarded research contracts to develop further and apply this test.

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.

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 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 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--increases 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 proved 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 developing 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 (ECMO) in acute, potentially reversible respiratory crises.

Limited progress is being made toward effective means of storing and transplanting lungs. From 1963 through December 1975, the American College of Surgeons/NIH Transplantation Registry recorded 37 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. Another recipient died of bronchial artery erosion and hemorrhage 6 months following lung transplantation.

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. Also needed is a practical method of preserving excised lungs prior to transplantation. 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. 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 and 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 casis of chronic bronchitis may be prevented."

Enzyme Deficiency Implicated

Population studies indicate that certain persons are genetically predisposed to chronic lung disease. A hereditary deficiency of an enzyme called alpha-1-antitrypsin predisposes some individuals to the development of a kind of emphysema and makes them more susceptible to the harmful effects of air pollution and 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. Such individuals are said to be homozygous for this characteristic. But the risk may still be substantial in heterozygotes--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 lung irritants, then a means of detecting these people may have value. But the recent discovery of more than twenty variant forms (phenotypes) of antitrypsin, including several different homozygous forms, 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.

Identified collectively as the protease inhibitor (Pi) system, the antitrypsins discovered thus far have been detected by a two-stage electrophoresis procedure whereby the enzymes migrate various distances in an electric field, first according to their electrical charge alone, then under the combined influence of their electrical charge and immunological affinity for antitrypsin antibodies in the test system. The enzymes have been classified and labeled alphabetically according to their relative mobilities in the electrophoresis test system. Thus, the most common phenotype, homozygous type M (designated Pi MM), possesses intermediate mobility, whereas the rare variant Pi ZZ migrates very slowly and travels but a short distance during the course of the test. Electrophoretic mobility of the heterozygous phenotype Pi MZ is intermediate between Pi MM and Pi ZZ.

Studies attempting to correlate differences in Pi phenotype with the occurrence of pulmonary disease are incomplete, but suggest that 4 out of 5 Pi ZZ individuals develop familial emphysema (and 10 percent fall victim to a form of infantile cirrhosis characterized by accumulations of antitrypsin in the liver). In this most severely affected group, victims typically develop emphysema before the age of 40, but occasionally during childhood. The studies also show that individuals of Pi SS, SZ, and PZ phenotypes are predisposed to familial emphysema, but the disease is less common and usually of later onset than in Pi ZZ individuals.

While still of a research nature, these screening programs will be expedited by the recent finding that accurate Pi phenotype determinations can be made after death (provided no blood was transfused within 72 hours before death), and by the development of a rapid, single-stage electrophoresis procedure that reduces the time required for phenotyping from 1-1/2 days with the old procedure down to 4 hours. Called isoelectric focusing, the new technique employs a different substrate and "finer tuning" of pH and electrical field to discriminate between alpha-1-antitrypsins and other alpha-1 protein components of albumin, thereby eliminating the need for the relatively slow antigen-antibody reactions to accomplish these separations. The isoelectic focusing technique also permits quantitative as well as qualitative studies, a decided advantage since circulating antitrypsins vary in amount as well as in kind among different individuals. For example, antitrypsin of the electrophoretically slow-moving ZZ type is present in an amount of from 10-40 percent of that found in the normal population (type MM).

Earlier structural studies of isolated antitrypsins suggested that molecular differences in the carbohydrate portions of the enzyme, notably a reduction in the number of sialic acid terminal groups, could account for both the low electrophoretic mobility and low circulating levels of some phenotypes. Investigators reasoned that the altered electrical charge of these phenotypes and their greater affinity for the plasma membrane of liver cells brought about their sequestration and accumulation within the liver to the detriment of circulating levels of antitrypsin.

But recent investigations show that variations in sialic acids are not solely responsible for the functional differences among antitrypsin types: these differences remained (albeit in reduced degree) in antitrypsins shorn of all their sialic acids by prior treatment with the enzyme neuraminidase. Moreover, a closer look at the antitrypsins (isolated in pure form only recently, using the aforementioned isoelectric focusing technique) revealed: 1) fewer sialic acid groups on the normal (type M) molecule than were previously thought to exist there, indicating a lesser magnitude of carbohydrate differences among the antitrypsins; and 2) differences in the primary amino acid structures of the M and Z molecules that may help explain the functional differences between them.

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. Futhermore, 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. Conversely, a deficiency or absence of other protease inhibitors that may act in concert with alpha-1-antitrypsin may be a secondary factor in the development of familial emphysema.

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 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.

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 City, 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 in any 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 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 on the production and destruction of collagen and other connective-tissue components 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 lungs, 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 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 (commonly known as "the heaves") 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 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. 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.

HEALTH SERVICES ADMINISTRATION

Bureau of Medical Services

Emphysema and Related Diseases

All eight general hospitals and the outpatient clinics within the Division of Hospitals and Clinics are engaged in the diagnosis and treatment of emphysema and related pulmonary disorders. Six hospitals, namely those in Baltimore, Boston, New Orleans, San Francisco, Seattle, and Staten Island maintain inhalation therapy clinics and provide more extensive clinical services and training activities.

The outpatient department of the Baltimore PHS Hospital offers an extensive battery of multiphasic medical screening examinations including spirometry. During the past year, spirometry screening examinations were performed on approximately 2,000 outpatients, 21.9% of which were abnormal, requiring referral for appropriate clinical follow-up procedures. Chronic obstructive pulmonary disease ranked fourth among those diagnoses which were newly established as a result of the multiphasic testing program at the Baltimore Hospital.

Research on emphysema-related respiratory diseases is included in the ongoing programs of clinical investigations sponsored within the hospitals of the Division. Related studies presently underway include a clinical study of the effectiveness of Defamadole in respiratory and soft tissue infections and a clinical trial of Nicotinamide in the treatment of asthma.

THE EPILEPSIES

In spite of its protection by the skull, the human brain suffers many insults from birth trauma, fevers, drugs, alcohol, and head injuries. When such insults cause brain damage, there often occur abnormal and undesired electrical discharges of brain cells (neurons) in affected brain areas. The discharges may cause brief episodes of unconsciouness, uncontrolled body movements or erratic behavior in various combinations. Such manifestations are called seizures. If seizures recur, they are called epileptic seizures and the person experiencing them is said to have epilepsy. Because there are many different kinds of epileptic seizures resulting from many diverse areas of brain injuries, we often talk about "the epilepsies."

The voluntary health organization dedicated to epilepsy is the Epilepsy Foundation of America (EFA). EFA estimates the number of epileptics in the United States as four million and the cost of their disabilities to the country at $4.25 billion a year. Other medical groups estimate one to two million cases and a somewhat lower total cost. Some $325 million are spent by the Federal government for aid, rehabilitation benefits, medical assistance and veterans care and about $85 million are spent by state and local governments for special education and other programs. Somewhat less than $10 million goes for the search for causes, prevention and improved treatment for these disorders.

Some 60 percent of epileptic patients can live relatively "normal lives" because their seizures are controlled by drugs or surgical removal of damaged brain tissue. The other 40 percent go partially controlled or without any control. Even those who have only a few brief attacks a year find it difficult, often impossible, to get jobs or drivers' licenses. Those who have frequent seizures have trouble existing without help. Gaining complete seizure control for all who have epilepsy is an important goal.

To increase the number of controlled cases of epilepsy, much basic and clinical research is conducted and supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), a component of the National Institutes of Health (NIH). Much of that research aims at finding more effective and less toxic anticonvulsant drugs than are now available.

This year the Institute implemented two new concepts for making that research pay off faster. Comprehensive Epilepsy Centers were set up by contract at three important medical centers for the primary purpose of getting research results to the patients who need them as fast as possible. And a new anticonvulsant drug screening project was added to the Antiepileptic Drug Development Program to study more drugs.

Obligations for Programs in the Epilepsies

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health					
National Institute of Neurological and Communicative Disorders and Stroke	$4,035,000	$5,610,000	$9,527,000	$9,582,000	$10,092,000

NATIONAL INSTITUTES OF HEATLH

National Institute of Neurological and Communicative Disorders and Stroke

Background

Our brains are constantly working, receiving information from inside and outside our bodies by way of our sense organs and their nerve networks. The brain sorts that information, evaluates it, stores some of it for future reference and acts on the rest through a network of motor nerves to our muscles.

To keep this intricate mechanism working, brain cells (neurons) generate electrochemical energy impulses which sweep rythmically along the neuronal networks. When there is a job to be done, neurons which control the brain or body part to be activated send impulses until the work is finished, then "turn off." Sometimes, in some brains, some neurons or groups of them don't shut off when a job is done, but keep sending action messages. When these excessive impulses continue, the body or brain parts on the receiving end operate erratically and the brain may even shut down conscious operation although in some cases, normal movements can continue without apparent purpose. Sometimes, adjacent neurons get excited and send additional unnecessary impulses involving the whole body in erratic movements. These fitful physical and mental activities are seizures. When they happen repeatedly, the brain parts where they originate are termed "epileptic" and the person is said to have epilepsy.

Seizures are classified as simple partial, complex partial, generalized and partial, secondarily generalized. Simple partial seizures are usually without loss of consciousness and consist of flickers, shakes, jerks of body parts, dizziness, or unpleasant sight, sound, taste, or stomach sensations. Complex partial seizures are usually with loss of consciousness where the individual appears to be in a dreamy state, at rest or moving automatically and purposelessly. He or she may also show outward signs of fear, anger, elation, or irritability although there is usually no memory of such feelings later.

In generalized seizures, most of the brain becomes involved, unconsciousness occurs and both sides of the body react. Such seizures are classified as absence, tonic-clonic, tonic, clonic, myoclonic or akinetic.

Sometimes partial seizures progress to generalized seizures, as nearby cells join the malfunctioning cells in the uncontrolled discharges until the whole brain and then the entire body are involved.

Seizure frequency varies from seldom to often. Seizures may last from a split second to several minutes. In "status epilepticus," they follow one another so closely that they appear continuous and can be fatal unless stopped by therapy. Seizures may be preceded by "auras" and are often followed by periods of exhausted confusion.

Causes

It appears that brain damage is basic to epilepsy. Difficult births, high fever, some infectious diseases, head injuries and chronic drug or alcohol addiction are often followed by seizures. Accidental or surgically-associated brain injuries can cause seizures in man. In animals, they can be caused by various experimental chemical or electrical stimulations. They often accompany brain tumors, abscesses or inborn brain malfunctions. Where no brain-injury possibility can be cited, the epilepsy is termed idiopathic (cause unknown).

Persons who have epilepsy but no other brain damage are as intelligent as the general population and have similar abilities for learning and working. Epileptics are not insane nor is epilepsy contagious. Susceptibility to epilepsy may be hereditary in some cases. More than half of the epilepsy cases are in people under 20. Yet, through brain injury, anyone can become epileptic at any age.

Therapy--Drugs and Surgery

Phenobarbital, first used for epilepsy in 1912 and diphenylhydantoin (Dilantin), developed in 1938, are still the most effective and safest drugs for controlling seizures. (Diphenylhydantoin was officially designated phenytoin in 1975 by U.S. Pharmacopia). There are 15 standard drugs for oral, long-term treatment of epilepsy, several of which are also useful for stopping "status epilepticus" when injected intravenously. Two of the drugs--carbamazepine (Tegretol) and clonazepam (Clonopin)--were approved by FDA for epilepsy treatment in 1974 and 1975 after a period of 14 years during which no new antiepileptic drugs had been introduced.

Surgery has been used to treat complex partial epilepsy but only in cases where seizure control is poor and where removal of affected brain areas will not cause more epileptic brain damage or impair other functions. Such surgery has provided invaluable knowledge toward better understanding of normal and abnormal brain functions. Surgical implants of devices which stimulate brain areas electrically have also been made experimentally. Long-term studies of the results of these procedures have not been sufficiently determined to establish whether or not they are beneficial treatments.

Research Tools

The electroencephalograph (EEG) which uses electrodes pasted to the scalp (or in some experimental cases implanted in brain cells) measures intensities and durations of brain waves. When used to locate the beginnings of epileptic discharges and follow their progressions, the EEG is the most useful tool yet developed to diagnose and conduct research on the epilepsies. Mobile EEG equipment which patients carry with them during routine activities holds electrodes in place and sends brain wave information via radio transmitters or wires to be tape recorded. Accurate records of seizures obtained this way before and after drug treatments help to evaluate efficacy. They also make possible repeated review and computer analysis of brain-wave patterns, thus aiding the development of devices that warn patients of impending seizures. Animal models in which seizures similar to those experienced by humans are induced by electrical, chemical or sensory stimulation, allow study of basic brain mechanisms and evaluation of new drug or surgical treatments. Gas Liquid Chromatography (GLC), and radio immuno-assay techniques are used to measure levels of antiepileptic drugs in patients' blood, allow scientists and physicians to maintain effective, non-toxic drug levels, verify whether or not a patient is taking prescribed

medicines and compare drug effectiveness and patient responses. Split-screen television techniques provide researchers visual records of EEG tracings, full-body views and face-closeups simultaneously during various types of seizures.

Epilepsy Research Projects

The Institute supports epilepsy research projects at the University of California at Los Angeles, the University of Washington, the University of Wisconsin, Yale University Medical School, Baylor University and Stanford University. Each center focuses on specific research aspects generating new knowledge about brain mechanisms and functions, and developing new treatment techniques. Additionally, NINCDS supports 65 other epilepsy research projects in 23 states and 2 foreign countries.

Perinatal Research

Since 1959, NINCDS has collected data on mothers and babies in over 50,000 pregnancies. This comprehensive effort, conducted through contract medical centers, aims at learning more about the causes of many neurological disorders, including the epilepsies. Data collection by the Collaborative Perinatal Project was completed in 1974, and analyses are in progress. Early results are becoming available. The frequency of convulsive disorders in children from birth to seven years is now known and will be presented soon.

Seizures occurring in the first week of life are a serious problem. Although some survivors of neonatal seizures are apparently normal, the occurrence of such convulsions is associated with a much heightened risk of death or later disability.

The most common convulsive disorder in childhood is febrile seizures. Subsequent development of chronic epilepsy occurs in 2-3 percent of those children who have febrile seizures. Identification of risk factors for epilepsy and for other unfavorable outcomes in this group of children is approaching completion, and should provide a more rational basis for decisions as to chronic treatment in the 2-5 percent of American children who experience at least one febrile seizure.

Epilepsy is more common in individuals of lower socioeconomic status. Factors which may underlie this association are under examination. Many other medical and social factors are under study in an effort to find means for prevention of the epilepsies.

Comprehensive Epilepsy Research Centers

On June 30, the Institute formally initiated three Comprehensive Epilepsy Research Centers through contracts at the University of Minnesota Health Sciences Center; the Good Samaritan Hospital and Medical Center in Portland, Oregon; and the University of Virginia Medical Center. These centers aim to assure the application of research findings to patients as quickly as possible and to assist clinical research by finding those patients most in need of new techniques. The programs are expected to facilitate clinical research and to coordinate research and teaching with health care services for persons with all types of epileptic seizures within a defined geographical area for each center. More than $2 million were made available to the centers for fiscal year 1976. It is hoped that the programs, which have five-year projections, will serve as models for research in other neurological and communicative disorders. Extensions of the concept in epilepsy are expected in the current fiscal year through awards of additional contracts.

Commission for the Control of Epilepsy and its Consequences

The Health Services Act (P.L. 94-63) became law in July 1975. Section 264 of that Act directs the Secretary of the Department of Health, Education, and Welfare to appoint a nine-member National Commission to conduct a one-year study on epilepsy and the way in which the nation is currently approaching it, and to report its findings to Congress. The resulting Comprehensive National Plan for the Control of Epilepsy and its Consequences will contain specific recommendations for research, treatment, and socioeconomic and rehabilitation efforts. The Commission began its deliberations early in 1976.

Drug Research

About five years ago, after establishing that few clinical evaluations of antiepileptic drugs had used scientific methods, the Institute began scientific evaluations and comparisons of the efficacy of currently-used and newly-introduced anticonvulsants. The Epilepsy Branch of the Institute's Neurological Disorders Program coordinates most of the nation's research in these areas. This research is guided by an NIH Advisory Committee on the Epilepsies, composed of physicians, pharmacologists and other specialists from medical schools and the drug industry.

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 of data from NINCDS supported studies, two drugs were approved for epilepsy treatment within the past year after 14 years during which no new antiepileptic drugs had been introduced. Carbamazepine (Tegretol) and clonazepam (Clonopin) received Food and Drug Administration (FDA) approval in August 1974 and June 1975 respectively. Data from Institute studies at the New Castle State Hospital, New Castle, Indiana, were included in the CIBA-GEIGY Company's application to FDA for approval of Tegretol. The NINCDS-supported studies of Clonopin at the University of Virginia; Medical College of Wisconsin, Milwaukee; and Medical College of Georgia, Savannah; contributed to the Roche Company's application for approval of that drug.

In late 1974, the Abbott Company obtained rights to valproate sodium (Depakine), also called dipropylacetic acid sodium, which has been used extensively in Europe and Japan for some 10 years. Abbott filed an Investigative New Drug Application with the FDA in December 1974. The Institute is cooperating with Abbott in obtaining safety and other data of the drug's use in adults at the University of Virginia and at the NIH Clinical Center. Foreign use of the drug has shown it effective against a variety of seizures without serious side effects. Early in 1976, pilot studies in children and double-blind tests in children will determine whether or not the drug is effective against absence seizures.

Another Abbott Company anticonvulsant, clorazepate dipotassium (Tranxene), already marketed in the U.S. as a tranquilizer, has completed the pilot phase of its investigations. Studies are expected to begin early in 1976 under contract with the University of Washington to compare Tranxene's efficacy with that of phenobarbital when used as an adjunct to Dilantin in treating complex partial seizures. These studies are scheduled to end by June 1977. Sound information should be obtained from the studies on the relative anticonvulsant value of the benzodiazepines as a class of drugs.

Pilot studies have been completed on the use of mexiletine (Ko 1173) in institutionalized populations at the University of Florida, Gainesville, and the New Castle State Hospital, New Castle, Indiana, as an adjunct with other drugs in control of various seizure types. Preliminary results of those tests are in Epilepsia. The drug, product of C.H. Boehringer Sohn, Ingelheim, West Germany, has also been evaluated in the same patient population at New Castle in a double-blind procedure with crossover. While the results are still undergoing analysis, preliminary tabulations indicate that Ko 1173 may be valuable to some patients as an adjunct to their usual medicine.

Four American drug firms not presently marketing anticonvulsants are now conducting animal experiments which may lead to clinical studies of novel drugs, i.e. new drug groups or drugs of new chemical structure. This interest, evidence of recognition of the growing importance of anticonvulsants, is encouraging to Institute personnel as it may be due partly to their programs and efforts over the past seven years to find and stimulate the search for new antiepilepsy medication.

At the University of Washington, comprehensive reviews were made of data gathered in 18 months comparing the effects on behavior of carbamazapine and phenytoin when used for complex partial seizures. Results indicated that, contrary to expectations, a streamlined battery of currently available behavioral tests will not work and that more effort is needed to devise test batteries that will make such drug-behavioral evaluations meaningful.

Effectiveness of carbamazepine and primidone in patients receiving phenytoin were compared in a study at the Lafayette Clinic, Detroit, Michigan. The drugs showed approximately the same effectiveness as measured by seizure frequency. Side effects resulted from the drugs. EEG findings and results from behavioral studies are still being analyzed.

A University of Kansas pilot study continues probing whether or not the number of post-trauma epilepsy cases can be reduced by immediate and extended treatment of head-injury accident victims with phenytoin and phenobarbital. By mid 1975, 125 patients had entered the program. Trauma severity was divided into four classes. Initial doses in amounts deemed "prophylactic" were given intravenously, followed by equivalent daily oral doses for 18 months. Half the patients received placebo. Patients were then followed for an additional 18 months without using medicine. The study will end in mid 1978 when the last patient to enter will have been observed for 36 months. Seizures have occurred in both groups; however, no statistical conclusion can be made until data on the last patient are in.

Since mid 1975 at the National Institutes of Health Clinical Center, a pilot clinical research program has been underway. The efforts are twofold: seizure monitoring, video tape recording of seizures, regular and telemetered EEG recordings and drug-level measuring; and pilot evaluations of valproate sodium. Complex partial seizures in persons having severe epilepsy are of particular interest. All the Institutes' tools for epilepsy research (most of them developed by NINCDS) will be focused on treatment of patients entering this program.

Since July 1974, the National Bureau of Standards has been developing (under an interagency agreement with NINCDS) standard reference materials of phenytoin, phenobarbital, primidone and ethosuximide in a biologic matrix to assure that commercial laboratories all produce similar, reliable drug-level measurements. The program is proceeding on schedule and the standards should be ready by July 1976.

The Epilepsy Branch's pharmacology laboratory continues studying how antiepileptic drugs affect the brain, how drug combinations work and how to measure blood levels and metabolites of both standard and experimental drugs used in current investigations. This year the laboratory acquired a gas-chromatograph mass-spectrophotometry computer system. The device allows precise identification and quantification of all metabolites of any drug and makes possible the study of the half-life of drugs in patients receiving anticonvulsants without medication withdrawal. And, acquisition by the Branch of a mini-computer system promises important improvements in several aspects of the Institute's epilepsy research programs.

On January 1, 1975, NINCDS began the Anticonvulsant Drug Screening Project as a new part of the Antiepileptic Drug Development Program which has been in progress since 1968. The Project is to identify new novel anticonvulsant compounds, and to use the information gained to predict what compounds may be good anticonvulsants. The program is generating within the pharmaceutical industry renewed interest in the synthesis of anticonvulsant compounds in the development of antiepileptic drugs. Under the project, the Epilepsy Branch registers and reviews the compounds received, determines if they are new to the project and notifies suppliers if compounds of the same structure have already been tested. At the University of Utah, through contract, the drugs are tested on appropriate animal models and classifed according to their anticonvulsant activity and neurotoxicity. Sources are industry and universities. So far, fewer compounds have been submitted than had been expected, but more compounds than expected are being found with anticonvulsant potential. Although the contract with the University of Utah runs only until mid 1976, new compounds will continue to be evaluated as long as they are submitted.

Experimental Animal Studies

Much has been learned about the structure and operation of the brain through basic brain research. Studying abnormal brain states like the epilepsies helps us to learn more about normal brain functions. One way to study epileptic abnormalities and to test drugs for treating them is creation of animal epileptic models.

Various chemicals alien to animal bodies when placed on or in animal brains cause local reactions (foci) which later produce recurring seizures like those of human epilepsy patients. The most commonly used chemicals are cobalt, alumina cream and penicillin which cause epilepsy-generating brain damage. This year several experiments that tested drug effectiveness or sought basic epilepsy mechanisms in chemically induced animal epilepsies were reported.

Investigators at the University of Washington, using Rhesus monkey models in an 8-month experiment, tested the effects of phenytoin, phenabarbital and primidone on spontaneous complex partial seizures. They found all three drugs effective in the model with minimal side effects. Their results correlated closely with data collected on similar tests with humans. They concluded that this model and their systems for recording animal seizures are excellent for testing new anticonvulsants and for further exploration of cyclic mechanisms of epilepsy.

At McGill University and the Montreal Neurological Institute, Montreal, other researchers performed similar experiments using cats with penicillin-induced generalized seizures to compare the efficacy of ethosuximide and phenytoin. They found that in this model ethosuximide gave better responses than phenytoin and that the ethosuximide responses were in accord with clinical experience in similar human epilepsy cases. They concluded that the model is potentially useful for screening anti-epilepsy drugs, and that ethosuximide may affect some fundamental epileptogenic mechanism common to a variety of seizure forms.

If the mechanisms of action of anticonvulsants were known, the responses of a particular seizure type to various anticonvulsants would allow inferences concerning the physiologic mechanisms involved. And that is another use being made of animal models--to learn what really happens in a seizure and how drugs can affect the happenings. Grantees at the Johns Hopkins University School of Medicine, Baltimore, Maryland, initiated experiments in this direction. They induced complex partial seizures in Rhesus monkeys to study the basic mechanism of these seizures in a model as similar as possible to human seizures. With implanted depth electrodes, as well as surface electrodes, they charted the spread of the epileptic electrical activity in the brains of the monkeys. They observed the natural sleep effect on the epileptic activity, the clinical manifestations (including autonomic responses during seizures), seizure activity and its spread, and other electrical occurrences.

Studies of the effects that cooling has on normal and alumina and penicillin-induced epileptic brain cells in cats were conducted by grantees at the University of Washington. Recording intracellular activity while lowering the temperature of the cats' brains, they discovered various intrinsic abnormalities in the "epileptic" cell membranes which affect the potassium-sodium ionic balance of those cells. The transfer of those ions between cells appears to be important to seizure activity. The investigators concluded that the electrical bursts which cause seizures may originate intrinsically within the abnormal cells, and that drugs which influence passive ionic exchange or active sodium-potassium transfer may be useful therapy in human epilepsy.

And, at Temple University, Department of Pharmacology, experiments in sensory stimulation were conducted with rats. Scientists gave a seizure-causing chemical, flurcethyl, to both normal and brain-damaged rats, then exposed them to photic and audio stimulation. They found that both types of stimulation and also brain-damaging lesions lowered seizure resistance. However, when both photic and audio stimulation were presented simultaneously, seizure resistance to the chemical returned to normal. And, when audio stimulation and brain damage were combined, resistance returned to normal. The experiments corroborate past reports of the effect of environmental stimulations in precipating seizures and suggest that this knowledge can influence seizure therapy. They established that brain damage also influences sensitivity to seizures.

Treatment

Within the past decade a wealth of pharmacologic information has been accumulated for those antiepileptic drugs used most frequently. This information, together with the development and application of new techniques to measure blood concentration of the drugs has helped the physician to prescribe better the available drugs to control seizures more effectively. Physicians can determine if the correct amount of a drug is present (biologically available) within the body and can prevent many of the toxic side effects while improving the results of treatment. Without special counseling in the importance of medication, 10 to 20 percent of patients fail to take their antiepileptic medication regularly and often unfairly blame the drug for lack of success. Furthermore, the epileptic patient often takes other drugs for the treatment of other conditions, influencing the levels of antiepileptic drugs in the blood through drug interaction.

Essential pharmacologic data for the four most commonly used antiepileptic drugs are now available and application of these data can improve clinical care. Phenytoin is poorly soluble and is hardly absorbed in the stomach. When injected into muscle, it is absorbed slowly and often causes muscle irritation. Consequently, the absorption of phenytoin has a greater variation among patients than does that of phenobarbital, primidone (Mysoline), and ethosuximide (Zarontin). Since the average time for elimination of half the amount of an absorbed dose is 24 to 30 hours, Dilantin may be given twice a day rather than three times a day. If treatment is being initiated with the regular dose of Dilantin, steady state blood levels will not be reached for 5 to 7 days. If it is clinically urgent to

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have complete coverage by antiepileptic medication, intravenous or oral loading doses should be given.

Treatment is an individual matter because of the marked variation between patients in metabolising any drug and patient's sensitivity to the drug. Because of this marked individual variation and the fact that reliably determined blood levels are a better guide than dose, the physician needs to know the blood level of the antiepileptic drug.

Surgical

Stimulation of the brain for control of seizures has been tried as a method of therapy at some medical centers. Studies with animal models have shown that the cerebellum exerts inhibitory and regulatory influences upon experimental seizure activity. However, the mechanisms for control of seizures by cerebellar stimulation is not understood. It is also not known what characteristics of patients make them more likely to have successful results from these surgical procedures, what the optimal stimulation parameters should be, or what the ultimate long-term implications in man will be.

Animal studies indicate that tissue damage to the cerebellum does occur with chronic stimulation but that there are no signs of cerebellar dysfunction as a result of this damage. It has been suggested that different schedules of stimulation may reduce the amount of damage produced. Until further studies are completed the ultimate usefulness of cerebellar stimulation will not be known.

Diagnosis

The EMI scan is considered a major advance in diagnostic medicine. The scan is non-invasive and relatively easy to perform. Its major usefulness has been in diagnosing brain tumors and other mass lesions. The usefulness of the EMI scan in epilepsy is just starting to be explored.

Epidemiology

Epilepsy epidemiologic research is greatly hampered by lack of information about the number of epileptics in the country, and the number of new cases which develop each year. Because epilepsy is not a reportable disease and because so many persons who have it hide their condition to avoid accompanying social ostricisim and employment discrimination, reliable data is difficult to obtain. Numerous efforts in this direction have not been sufficiently large and diversified to provide the needed information. Now, the Institute's Office of Biometry and Epidemiology plans a large and comprehensive study of the country's epilepsy population to establish meaningful figures on prevalence, incidence, and cost. Two years of pilot studies will begin early in 1976. The work will be coordinated with that of the Commission for the Control of Epilepsy and its Consequences. The actual survey, expected to take at least two years, should get underway early in 1978.

One of the first and best reported studies of the epidemiology of epilepsy in a community was conducted in Rochester, Minnesota, by Dr. L.T. Kurland in 1959. This study has now been extended and updated to cover the time period 1935-1967. The mean annual incidence rate in Rochester is 48.7/100,000 population. The pattern of age-specific incidence rate was highest in the first year of life, low and fairly constant in middle age, and higher again at advanced ages. The lifetime prevalence rate (cumulative risk, i.e. prevalence of all patients who at any time had had two or more recurrent afebrile convulsions) was approximately 6.7 and 6.5 per 1,000 population on January 1, 1960 and January 1, 1965 respectively in Rochester.

The influence of epilepsy on life expectancy is of particular importance since it is difficult for epileptic persons to obtain life insurance.

To determine the influence of epilepsy on life expectancy, survival among the 516 cases diagnosed in Rochester in the 33-year study period was expressed as a percentage ratio of survival among a group, matched by sex and age (at diagnosis), derived from the Minnesota life tables. For the entire study group of 516, the survivorship ratio was 95 percent at 5 years, 90 percent at 10 years, and 89 percent at 15 years post diagnosis. Patients whose diagnosis was made before 1945 had no significant difference in survivorship ratios. In the group diagnosed after 1945 (which included a higher proportion of patients with partial seizures), overall survivorship was 88, 84, and 81 percent at 5, 10, and 15 years post diagnosis, respectively. Patients with seizures thought to be temporal in onset or absence seizures, and patients whose epilepsy was diagnosed between ages 1 and 20 years, had no significant alteration in survivorship from that expected.

Evidence has been accumulating during the last few years that some anti-epileptic medications may have a teratogenic effect. A study of 284 births in Rochester, Minnesota, to 138 women who had epilepsy suggests (as have other studies) that there is an increased incidence of malformations among the offspring of women taking antiepileptic drugs. Nevertheless, the relative contribution of the medication and other risk factors to an increased rate of malformations remains unclear. Other risk factors may include type and severity of seizures during pregnancy, other unrecognized factors associated with epilepsy, and genetic factors. The way antiepileptic drugs produce malformations is not known. Research here is urgent because it is difficult to see how any major changes can be made in the present epilepsy treatments of fertile females.

COMMUNICATION

Knowledge gained from research is valuable only when it is applied to those who can benefit from it. To insure rapid and clear communication of epilepsy research results to scientists and physicians the Institute has done several things.

1. NINCDS contributed (a) considerable editorial and administrative effort to publication by Raven Press of "Complex Partial Seizures and Their Treatment," Volume 11 in their Advances In Neurology series and (b) assistance in manuscript development for another Raven Press offering this year, "Science and Epilepsy, Neuroscience Gains In Epilepsy Research."

2. NINCDS continues partial funding of the monthly Epilepsy Abstracts, now in its eighth volume. It is used by over 1,000 subscribers who pay Excerpta Medica about $50 a year to help defray costs of publication and mailing.

3. NINCDS sponsored a meeting in May 1975 of the NIH Epilepsy Advisory Committee and two meetings, one in March and one in September, of the Subcommittee on Anticonvulsant Drugs. They reviewed progress of Institute-sponsored research and recommended proposals for continued and additional studies.

4. Sponsored a July meeting of the Basic Research Subcommittee at Yale University Medical School. Discussion centered on the need for more information about the way that antiepilepsy drugs work. Another meeting is scheduled for February 1976 at which recommendations for a workshop on this subject will be made.

5. Sponsored a May workshop on infantile spasms at the National Institutes of Health to discuss clinical aspects, natural history, EEG aspects, quantification, etiology and treatment. Workshop recommendations set directions for infantile spasms research. The Institute plans to implement the workshop recommendations.

6. NINCDS continued sales through the National Audiovisual Center and free loan-distribution by the National Medical Audiovisual Center of a motion picture, "The Absence Seizure." The film shows all types of absence seizures and their EEG patterns and emphasizes the importance of correctly diagnosing absence so that the most effective therapy can be applied. Over 72 loans and 25 sales of the film were made during 1975.

7. NINCDS cooperated in the production of a motion picture on complex partial seizures filmed by MEDED Projects, Roselle, New Jersey, under an educational grant from the CIBA-GEIGY Company.

8. NINCDS, through its Office of Scientific and Health Reports, responded to requests from the scientific, medical, paramedical and lay public for 8,200 epilepsy pamphlets, monographs, magazine reprints and for specific personal information. Materials for general public inquiries included Epilepsy, Hope through Research in both English and Spanish and NINCDS 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 announcements and TV appearances by Institute scientists also generated interest in the publications and work of the NINCDS.

HEMOPHILIA

Hemophilia is a term usually reserved for the two most common forms of hereditary hemorrhagic disease: hemophilia A, or classic hemophilia, and hemophilia B, also known as Christmas disease. The term also embraces, however, some twenty additional disease entities including one--von Willebrand's disease, formerly known as "pseudohemophilia"--that may prove to be the most prevalent form of hemophilia. All the hemophilias are characterized by deficiencies in the amount or activity of certain blood clotting factors that can lead to uncontrolled bleeding.

Although these deficiencies may be mild and of little or no clinical significance in many hemophiliacs, moderate to severe clotting factor deficiencies in approximately 20,000 Americans pose a constant threat of hemmorhage, crippling, and premature death.

National Heart and Lung Institute (NHLI) research programs directed against hemophilia and other hemorrhagic disorders include basic studies of clotting factors in health and disease; development of improved methods of detecting, diagnosing, and evaluating the disease in its active and carrier states; devising new and improved forms of therapy for victims of hemophilia involving the modification or replacement of deficient clotting factors; basic studies of clinical significance or the nature of clotting factor inhibitors; and research to enhance the safety, effectiveness, and availability of blood and blood products for the prevention and treatment of bleeding episodes.

The National Institute of Arthritis, Metabolism, and Digestive Diseases' Clinical Hematology Branch, and the Hematology Service of the Clinical Pathology Department, NIH Clinical Center, also conduct some research on hemophilia.

Obligations for Programs in Hemophilia

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes Of Health:					
National Heart and Lung Institute.....	$4,788,000	$6,402,000	$7,740,000	$7,500,000	$6,900,000
National Institute of Arthritis, Metabolism and Digestive Diseases.....	255,000	317,000	361,000	381,000	415,000
Clinical Center.....	15,000	20,000	57,000	56,000	56,000
Total, NIH.....	$5,058,000	$6,739,000	$8,158,000	$7,937,000	$7,371,000

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

Background

The coagulation of blood is a complex process involving many steps and the participation of at least eleven blood clotting factors. For a number of these clotting factors there are hereditary deficiencies or defects that may result in bleeding tendencies ranging from mild to very severe in affected individuals.

Known collectively as the hemophilias, these hereditary hemorrhagic disorders include:

- classic hemophilia, or hemophilia A, the result of a deficiency in functional factor VIII (antihemophilic factor, or AHF).
- hemophilia B--also called Christmas disease after the patient in whom the defect was first detected--caused by a deficiency of functional factor IX (Christmas factor).
- von Willebrand's disease (formerly known as "pseudohemophilia") recently shown to be the result of a defect in the factor VIII molecule distinct from that in classical hemophilia A.
- and other, less common forms such as hemophilia C, for example, a rarely encountered deficiency of factor XI (plasma thromboplastin antecedent, or PTA) that afflicts primarily people of Jewish ethnic origin.

Their diversity, both as to type and degree of severity, foils attempts to determine the prevalence of the hemophilias in the population. Clotting factor deficiencies are mild and of no clinical significance in many hemophiliacs and, as no overt bleeding tendency exists, often go undetected. In others, clotting defects are detected only after an automobile accident, dental extractions, surgery or other major trauma elicits severe, often uncontrolled bleeding,

An estimated 20,000 Americans suffer from severe hemophilia. About 15,000 of these have hemophilia A, some 5,000 hemophilia B, and an undetermined number have von Willebrand's disease, which is a relatively mild bleeding disorder in most.

Both hemophilia A and hemophilia B affect males almost exclusively, but are nearly always transmitted by female carriers. In these sex-linked forms of hemophilia, if a male hemophiliac begets children, his sons will be normal, but his daughters will be carriers. But if the daughters bear children, their sons have a 50-50 chance of being hemophiliac and their daughters a 50-50 chance of being carriers. Hemophilia can occur in women, but this is rare because it requires a union between a hemophilic male and a female carrier. Daughters born of this union have a 50-50 chance of being hemophiliacs and those who escape the disease will be carriers. Sons born of this marriage have a 50-50 chance of being hemophiliacs.

Von Willebrand's disease is inherited as an autosomal dominant trait. As such, it can affect, and be transmitted by, either sex, though it tends to occur more frequently in women. Thus, there appear to be two separate sites of genetic control of the factor VIII molecule.

About 30 percent of all cases of hemophilia apparently occur de novo, with no previous family history of the disease. Some of these cases probably represent errors or omissions in reconstructing the victim's family tree, but others may

represent recent genetic mutations. At present, it is impossible to determine which of these possibilities obtains in most instances of "unexplainable" hemophilia.

In victims of hemophilia, the chief threat to health or life is not excessive blood loss from surface cuts, abrasions, or related injuries. Bleeding from such causes can usually be staunched even if the coagulation defect of hemophilia remains uncorrected. The real threat is internal bleeding into organs, soft tissues, and joints, which may occur with no apparent reason in severe hemophilia and is very likely to follow even seemingly minor trauma. The only effective means of controlling such bleeding episodes is to supply the specific clotting factor needed to correct (temporarily) the victim's coagulation abnormality.

The major causes of death among hemophiliacs are thought to be cerebral hemorrhage and severe internal bleeding due to trauma, but there are no reliable data on this. The major causes of permanent disability in these patients are orthopedic problems resulting from repeated hemorrhages into the joints. These may result in progressive muscular atrophy, unstable joints, and related conditions that may eventually prove crippling.

In addition to all the other miseries that hemophilia visits on its victims and their families are the heavy financial burdens imposed by the disease. For the treatment of severe hemophilia, the cost of blood products alone may exceed $6,000 a year. Physicians' fees and hospital expenses average about $2,000 a year.

Current NHLI programs directed against hemophilia include basic research on antihemophilic factor and Christmas factor, their precise role in coagulation, the normal molecular structure of these factors and the genetic alterations occurring in hemophilia that cause them to perform poorly or not at all in clotting. Other research seeks possible means of stimulating the production or slowing the metabolism of normal factor VIII or IX in hemophiliacs or finding other substances with procoagulant activity that might be modified to substitute effectively for the normal clotting factors in victims of the diseases.

Applied research is concerned with improved techniques for extracting concentrates of factor VIII and factor IX from whole blood or plasma, finding means of eliminating hepatitis virus or other dangerous organisms from these concentrates, and improving techniques for detecting female carriers of hemophilia before they give proof of it by bearing hemophilic sons. A major cooperative study is seeking basic data on and effective means of dealing with antibodies against factor VIII that arise in some hemophiliacs, possibly as a result of repeated infusion or transfusion therapy. The inhibitor problem is considered by many to be a major obstacle in the management of hemophilia.

Diagnosis

Severe hemophilia usually becomes clinically manifest early and most cases are diagnosed during the first year of life. Mild or moderate hemophilia is more often diagnosed later because the victim may have sufficiently high clotting factor levels to prevent spontaneous bleeding episodes or other clinical manifestations of the disease under normal circumstances. Mild cases may not be detected until the patient bleeds excessively after trauma, a tooth extraction, or a surgical procedure.

Reliable coagulation tests have been developed that are practical for the routine screening of surgical candidates and which cover the possible gamut of clotting factor defects or deficiencies. Any abnormality in the results of these tests indicates that a clinically significant bleeding tendency exists even though it does not pinpoint the specific clotting-factor defect or deficiency responsible. However, this can be done by adding aliquots of plasma or plasma fractions known to be deficient in specific clotting factors to samples of the abnormal plasma, then repeating the coagulation tests. If the addition of plasma with the known clotting

factor deficiency fails to correct the abnormal test, the patient's plasma is also deficient in that factor.

These procedures for determining plasma concentrations of functional anti-hemophilic factor are useful both for the detection of hemophilia and for assessing the severity of the disease. For while AHF levels may vary widely among hemophilic patients, the lower the AHF level in the individual patient the greater his bleeding tendency. These assay procedures are also of great value in monitoring the effects of AHF infusions to prevent or control bleeding episodes in hemophiliacs.

Treatment

The prevention and treatment of serious bleeding episodes in hemophiliacs improved dramatically during the sixties with the introduction of clotting factor concentrates that, administered by intravenous infusion, could temporarily restore normal coagulability to blood deficient in AHF or AHF activity.

This formerly had to be done with transfusions of fresh whole blood or fresh or freshly frozen plasma. To raise functional AHF levels sufficiently to achieve hemostasis or to "prime" the hemophiliac for necessary surgery or tooth extractions and to sustain these levels during healing frequently required so much plasma that the patient's circulation might be dangerously overtaxed.

The first AHF concentrate to become widely available was a cryoprecipitate prepared by a technique developed by Dr. Judith Pool and associates at Stanford University. They found that when fresh frozen plasma was slowly thawed in the cold, an AHF-rich precipitate was formed that contained, in concentrated form, upward of half the AHF originally present in the plasma. The precipitate could easily be separated and could be stored for extended periods at very low temperatures until needed. Almost any hospital blood bank can prepare AHF concentrates by this method.

Other AHF concentrates are prepared by using neutral amino acids, such as glycine, to precipitate AHF from plasma. Some of these use pooled batches of cryoprecipitate as the starter material and yield highly concentrated AHF that can be lyophilized, or "freeze-dried," to a stable, powdered form that can be stored under normal conditions for prolonged periods.

Cryoprecipitate is usually prepared from individual units of whole blood or plasma and may vary considerably in potency from one unit to the next. Each batch of powdered AHF from pooled plasma or cryoprecipitate can be assayed for potency, which will not vary among samples from that particular batch. This makes it easier for the physician to calculate the dosage of concentrate required for prevention or control of bleeding episodes. But the yield of AHF per unit of source plasma may be substantially less for powdered AHF than for cryoprecipitate and the cost per unit somewhat higher. The use of pooled plasma or pooled cryoprecipitates also increases the chances that the resulting AHF concentrate may contain hepatitis virus.

Most hemophiliacs receive episodic or "demand" treatment: that is, AHF concentrates are infused only when bleeding episodes occur or in anticipation of some dental or surgical procedure. The hemophiliac or some member of his family can usually be trained to administer such infusions at home at the first sign of bleeding. Very early treatment frequently reduces the amount of concentrate needed to control the episode and also reduces damage to the joint or other affected tissues.

Prophylactic care, in which AHF concentrates are infused regularly to sustain sufficiently high plasma levels to prevent most bleeding episodes, is beyond the means of many hemophiliacs. And even if the problems of cost could be solved, problems would arise in preparing sufficient amounts of concentrate for this purpose with current technology. Moreover, there is no solid data to show that it is better than demand therapy, and the consequences of long-term prophylactic therapy are not known (e.g., the risk of hepatitis).

Episodic care for hemophiliacs requires the collection of the equivalent of an estimated 3 million units of whole blood each year. (Some of the whole blood collected for the extraction of factor VIII is obtained by plasmapheresis, a procedure whereby the plasma is retained for processing, but the cellular components of blood are returned to the donor.) Depending on how one defines adequate prophylaxis, prophylactic AHF therapy could increase this annual requirment to as much as 13 million whole blood equivalents (roughly 75 percent of all blood and plasma collected each year) if cryoprecipitate were used for the purpose. If powdered AHF concentrates were employed, the requirements would be considerably higher because of presently unavoidable AHF losses incurred during the preparation of concentrates.

With the goal of increasing the availability of AHF concentrates and reducing their cost, NHLI continues to support research concerned with improving the efficiency of present methods of extracting AHF from plasma. Other research is concerned with the development of effective substitutes for human AHF. This includes studies seeking safe, non-antigenic AHF concentrates from pigs, cows, or other animal sources and the quest for other substances with procoagulant activity to carry out the role normally played by AHF in coagulation.

Another approach involves bypassing AHF altogether, by activating a subsequent step in the blood coagulation process. In connection with this, several NHLI-supported studies are investigating the value of activated prothrombin complex for normalizing blood coagulability in AHFdeficient patients. Clinical studies in patients with factor VIII inhibitors have been promising.

The factor VIII molecule is so large and complex that laboratory synthesis of this clotting factor appears unlikely. However, research on the structure of factor VIII reveals that the procoagulant activity resides in a smaller subunit or fragment of the molecule that may be more amenable to precise structural determination and to synthesis in the laboratory.

The large size and complexity of the factor VIII molecule also provides a plausible explanation for the great variety of hemophilic states encountered among different families afflicted with hemophilia A: structural defects can occur in a number of different sites within the molecule, with each defect affecting blood coagulability in a different way.

Similarly, in von Willebrand's disease, a major portion of the factor VIII molecule is missing, and this gross molecular defect correlates with the abnormal platelet function and distinctive clotting disorder seen in patients with this disease.

Other approaches under investigation include:

- introducing minor chemical modifications in the AHF molecule that will not adversely affect its activity, but which might slow its rapid clearance from the plasma. The half-life of infused AHF is only 8-10 hours and its disappearance is still more rapid during bleeding episodes.

- using inhibitors of fibrinolysis--the mechanism by which the body dissolves clots--as an adjunct to AHF therapy. Inhibitors such as epsilon amino caproic acid (EACA) may reduce AHF requirements in certain bleeding episodes by safeguarding needed clots from attack. Used in this way, EACA is especially valuable for safeguarding hemophiliacs during dental procedures.

- transplanting into hemophiliacs, AHF-producing tissues to help correct their deficiency of functional AHF: far out now, but a possibility.

Prevention

Female relatives of hemophiliacs are frequently concerned, as well they might be, by the possibility of transmitting the disease to their own sons. The female carrier of hemophilia is usually asymptomatic. In some instances, the asymptomatic carrier can be identified by application of what is known about the mode of inheritance of hemophilia together with a close examination of the potential carrier's genetic background.

For the sex-linked forms of hemophilia, detection of the carrier state solely on the basis of family history is fraught with difficulty. She must be a carrier, however, if: a) her father is a hemophiliac; b) she has borne one hemophilic son and has other affected relatives; or 3) she is the mother of more than one hemophiliac. In all other instances, it is impossible to be sure, on historical grounds alone, whether she is normal or a carrier; and the gathering of such historical data is often difficult or impossible.

About one-fourth of hemophilia carriers exhibit plasma levels of functional AHF sufficiently low for positive identification. In three-quarters of the carriers, the wide normal variation in AHF levels among different individuals, or even in the same individual at different times, makes the results of functional coagulation tests equivocal. Recently, however, Dr. Oscar D. Ratnoff and co-workers at Case Western Reserve University have developed methods that may identify carriers with an increased accuracy. This procedure is undergoing further study by a group of workers sponsored by the NHLI and the National Hemophilia Foundation.

Hemophiliacs synthesize both functional and nonfunctional AHF. The abnormal variant, which does not participate normally in clotting--and which does not show up in functional coagulation tests--comprises 90 percent or more of the total in moderate to severe cases. The abnormal variant can be detected, and its plasma concentration determined, by immunochemical techniques employing antibodies against factor VIII. The antibodies make no distinction between the two forms.

Carriers of hemophilia also synthesize both types of AHF, but the functional clotting factor comprises a considerably higher percentage of the total, so that functional coagulation tests may yield results within the normal range. If, however, the results of these tests are combined with those of the immunochemical tests, the presence of significantly high levels of nonfunctional AHF will identify the hemophilia carrier.

The proven carrier who is pregnant may have amniocentesis performed. By studying cells aspirated with some of the fluid surrounding the fetus in the womb, it is possible to determine the sex of the fetus. If the fetus is a male, however, the procedure cannot determine whether he will be hemophilic or normal. If the child is female, it cannot ascertain whether she is a carrier. And so the dilemma of whether or not to consider a therapeutic abortion remains. We are hopeful that the continuing quest for reliable genetic markers for hemophilia will soon eliminate the element of chance from such decisions.

Conclusion

The lot of the hemophiliac is much better today than it was only a few years ago. Unfortunately, it is still a wretched one, for the victim and for his family. It seems unlikely that the disease can be eradicated, nor are the expectations very bright for a cure during the near future. However, through continued research and the fullest possible application of new knowledge gained through such efforts, we can continue to reduce the physical, emotional, and financial burdens presently imposed by the disease.

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 rate of high blood pressure among U. S. blacks is about twice as high as that among whites, and the prevalence rate 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.

Probably, at least in part, due to the availability and widespread use of effective drugs for blood pressure control, the U. S. death rate from high blood pressure has declined more than 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 heart attacks and other manifestations 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, the risk from coronary heart disease is increased by a factor of 3.4. If, in addition, blood fats are elevated, the risk is more than 10 times that of persons with none of these risk factors.

Obligations for Programs in Hypertension

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health: National Heart and Lung Institute.....	$31,983,00	$40,983,000	$36,378,000	$47,426,000	$43,759,000

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

Hypertension

When the physician determines blood pressure with the familiar blood pressure cuff, two numbers are recorded. 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 as 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 as defined by 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 stable, climbs sharply to levels that pose an immediate threat to 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's job nor in other pursuits. However, all of the most effective antihypertensive drugs may cause undesirable side effects, including blurred vision, bladder dysfunction, constipation, anemias, liver disease, abnormal heart rhythms, 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 great 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 treatment was initiated by a physician.

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 longer periods for observation and larger numbers of patients followed under controlled situations to observe sufficient numbers of significant effects.

High blood pressure is easily detected in the physician's office. Yet, because the disease in its early stages seldom produces symptoms that send the afflicted person to a doctor, 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. Early research results identifying and testing non-drug therapies are inconclusive.

Current Research Efforts

The National Heart and Lung Institute (NHLI) currently supports more than 200 research projects at universities and medical centers all over the country concerned with etiology, pathogenesis, prevention, diagnosis and treatment of high blood pressure, and with related subjects, such as kidney disorders and physiology. 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 nervous system, hormones, and other biologically-active substances in regulation of blood pressure.

--Physiology and pharmacology of vascular smooth muscle in normotensive and hypertensive conditions.

--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 kidney hormones, such as renin, kallikrein, and prostaglandins in blood pressure control.

-- The kidney mechanisms operative in maintaining fluid, electrolyte, and acid-base balance, and disturbances in these mechanisms that may underlie or result from hypertension.

-- Identification of innovative methods of educating 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, Vanderbilt, Boston and Indiana Universities. These centers are conducting research on problems which include:

-- interactions between the sympathetic nervous system, renin-angiotensin, aldosterone, renal function, and sodium metabolism in the etiology and maintenance of hypertension;

-- studies of inheritance of hypertension and biochemical parameters;

-- comparison of surgical and medical treatment of renovascular hypertension;

-- isolation and characterization of pure renin;

-- pharmacology of propranolol and role of prostaglandins in hypertension;

-- the role of new mineralocorticoids in human and experimental hypertension;

-- the role of renin-angiotensin system and other humoral factors in the development of hypertensive vascular disease;

-- the identification and typing of hypertensive patients using endocrine profiles related to electrolyte metabolism;

-- development of treatments for hypertension based on specific physiologic alterations.

Other definitive information will be provided by the NHLI Hypertension Detection and Follow-up Program, established in 14 clinical centers where approximately 11,000 patients age 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 157,000 persons were screened to obtain 11,000 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: 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 smoking 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 age 35 to 57. Recruitment of the approximately 12,000 study participants will be completed in 1976 and the clinical phase of the trial in 1981.

National High Blood Pressure Education Program

In an effort to combat some of these problems, NHLI is participating in an educational effort involving 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 about the dangers of high blood pressure and the beneficial effects of therapy.

Although NHLI has been designated the 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 150 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, education 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 research 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.

A major program development in public education is a new relationship with the Advertising Council. The Council has undertaken a major campaign effort on behalf of the NHBPEP resulting in increased media use of hypertension educational materials ranging from television announcements to billboards and transit ads. Dollar value of free time is expected to more than double.

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 the High Blood Pressure Information Center which responds to public inquiries, develops and evaluates educational materials, distributes, free of charge, educational materials produced by the NHBPEP and other organizations, operates a Speaker's 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. The 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 a month with local communities.

National High Blood Pressure Month has been designated 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 Month (May 1975) resulted in reported screenings of approximately 146,067 persons with elevated pressures to their physician through the coordinating and educational efforts of numerous local community programs. This reflects a 48 percent increase in the number of persons screened and 52 percent increase in the number of persons referred over 1974. This increase reflects a markedly improved reporting system with data from 900 of the organizations who participated in High Blood Pressure Month, as compared to reports from 300 participating organizations the previous year. Media coverage reflected a 140 percent increase over the previous month 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 have occurred. After little change from 1964 to 1971, patient visits for hypertension and hypertensive heart disease markedly rose about 12 percent per year in 1972, 1973, and 1974; the first three years of NHBPEP activity. Overall, visits have increased over 40 percent from the time the NHBPEP was initiated to date. Visits for all diagnoses have increased only 16 percent in the period. Data from the Health Interview Survey and 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. Continued research undoubtedly will yield safer, more effective drugs for blood pressure control, that eventually lead to cures where now only palliative measures exist, and will help eliminate high blood pressure as a major cause of illness, disability, and death in the United States and around the world.

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 counteract 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, thus 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. Furosemide, a powerful new diuretic, is used extensively in the treatment of hypertension and is especially useful where the presence of long-standing hypertension has resulted in significant kidney damage. 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 similar drop in blood pressure. Triamterene acts directly on the kidney to induce sodium loss; but spironolactone has an exceptional and interesting mechanism of diuretic action. This drug is chemically related to one of the natural steriod hormones secreted by the adrenal gland, called aldosterone, and it competes for the hormone's position on receptor sites in the kidney thus cancelling the function of the natural hormone to conserve salt and water. Hence, sodium and water are lost from the kidney 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.

Rauwolfia compounds such as reserpine are long-acting drugs derived from a plant called Rauwolfia serpentina. They are 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

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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 can be a significant and serious complication in a minority of patients. But in combination with other drugs, rauwolfia compounds are extremely valuable against essential hypertension.

Some recent studies indicated a statistical association between breast cancer and use of reserpine. Other reports have found no such association. Further evaluation and investigation by the Food and Drug Administration are underway. However, it has been conclusively proven 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. Angina attacks, however, 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 valuable drug for moderate to severe hypertension.

Methyldopa is another effective and widely used antihypertensive drug. Originally, it was thought to act by entering the sympathetic nerve endings which control the degree of blood vessel constriction and replacing the transmitter norepinephrine with a less active "false transmitter" called methyl norepinephrine. Recent studies indicate that, in addition, it has effects in the kidney to reduce the formation of a renal enzyme called renin, as well as within the brain to alter central control of blood pressure. Its side effects are most often minimal, but rarely can be serious and include drowsiness, anemia and liver dysfunction.

Guanethidine is a very effective drug used predominantly in severe hypertension. Its mechanism of action also relates to effects on sympathetic nerves and its toxicity can include severe postural hypotension, a fall in blood pressure upon standing which can result in dizziness and fainting.

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. One of the fast acting ganglionic blocking agents, trimethaphan, is given intravenously, to acutely lower dangerously high blood pressure in hypertensive emergencies.

Diazoxide is another swift and powerful intravenous antihypertensive of great value for acute hypertensive crises. Although 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. Sodium nitroprusside is another immediately effective antihypertensive drug given by intravenous infusion in hypertensive emergencies. Although long known to be uniformly effective, it has only recently become commercially available.

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. A cautionary aspect to its use is the occurrence of a rebound phenomenon if a patient is suddenly taken off or goes off the medication.

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. It also reduces or prevents the release of renin from the kidneys. 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 AND URINARY TRACT DISEASE AND ARTIFICIAL KIDNEYS

The kidneys play a critical role in the maintenance of body functions. They remove the end products of metabolism (body chemical reactions) from the blood and perform a number of other essential physiologic processes. Uremia results when the kidneys are unable to remove sufficiently the body's metabolic wastes and thus perform their role in maintaining the body's homeostasis. End-stage kidney failure is the common final event of many different kidney and urinary tract diseases. Some 42,000 Americans die each year from irreversible kidney failure although the lives of an additional 10,000 persons are prolonged with treatment through a MEDICARE-funded program of dialysis with artificial kidneys and of kidney transplantation.

The National Institute of Arthritis, Metabolism, and Digestive Diseases is the focal institute at the National Institutes of Health for Kidney research and diseases of the urinary tract. It shares responsibility for certain specialized aspects of kidney research with the National Institute of Allergy and Infectious Diseases.

Obligations for Programs in Kidney and Urinary Tract Disease and Artificial Kidneys

	1973	1974	1975	1976 Estimate	1977 Estimate
National Institutes of Health:					
National Institute of Arthritis, Metabolism, & Digestive Diseases					
Kidney Disease....	$17,726,000	$18,852,000	$21,077,000	$21,410,000	$21,723,000
National Institute of Allergy and Infectious Diseases					
Kidney Disease....	1,188,279	1,341,877	1,419,465	1,375,000	1,487,000
Health Resources Administration:					
Regional Medical Programs	2,461,000	5,651,000	5,224,000	---	---
Total.....	21,375,279	25,844,877	27,720,465	22,785,000	23,210,000

NATIONAL INSITUTES OF HEALTH

National Institute of Arthritis, Metabolism, and Digestive Diseases
KIDNEY AND URINARY TRACT DISEASE AND ARTIFICIAL KIDNEYS

Research directed against kidney and urinary tract disorders is an important part of the overall program of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). Now in its twelfth year, the Kidney Disease and Urology Program has over 230 active research grants whose awards totaled $14.2 million during fiscal year 1975. More than three-quarters of these grants support basic investigations concerning kidney and urinary tract function and its relation to disease. Both fundamental and clinical studies are being conducted; these are aimed at improving understanding of the kidneys and advancing our ability to prevent, control, arrest or cure the various diseases of the kidney and urinary tract, through research grants and contracts at medical centers, universities, and industrial and development organizations across the nation.

KIDNEY AND URINARY TRACT DISEASE RESEARCH

Approximately one-half of all renal deaths result from three types of kidney and urinary tract disease -- infectious, immunologic, and hypertensive. To achieve a reduction in the number of these deaths, it is essential that researchers find better methods of preventive treatment, earlier diagnosis and more effective therapy through greater understanding of the basic causes and mechanisms of the disorders. The total program of research includes fundamental studies of the kidney and urinary tract, such as: kidney microstructure as related to function, control of sodium excretion, congenital malformation, 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 in other organ systems such as renal osteodystrophy (uremic bone disease) and anemia. While supportive measures for end-stage kidney disease, such as dialysis or transplantation, are life-saving and life-extending, the most desirable objective of kidney disease research is control and prevention.

Experimental Glomerulonephritis

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 salt and mineral 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.

Numerous studies are being conducted to attempt to explain the mechanisms responsible for the reduction of glomerular (sites of blood filtration in the kidney) filtration rate, for proteinuria and for altered control of sodium regulation in glomerular diseases in humans. Recent studies by NIAMDD grantee Dr. Alan Robson at Washington University in St. Louis show that patients with renal disease and proteinuria may have one of three basic types of permeability patterns: (A) a normal pattern, usually seen in patients with mild lesions or in those who have recovered from acute glomerulonephritis; (B) an increase in permeability so that larger molecules of a size normally held back in the blood pass through the glomerulus and are found in the urine. In addition, the clearances of molecules usually present in the urine in only small concentrations, are increased, a pattern frequently seen in patients with severe glomerulonephritis; (C) a decreased clearance of small molecules normally present in urine with a clearance equal to that of inulin (a vegetable starch used in tests to determine kidney function). In certain patients with renal disease, the clearance of these molecules never equals that of inulin; their clearance is sometimes reduced to 50% or less than that of inulin.

Even though abnormalities in glomerular permeability have not been correlated with specific pathologic abnormalities found in renal biopsy, permeability patterns may change spontaneously during the course of the disease process, or as a result of the administration of drugs. Preliminary reports of studies of experimental glomerulonephritis in animals indicate that steroid therapy may correct patterns of glomerular permeability and may improve both renal function and the subjects' chances of survival.

Serum Immunoglobulins in the Nephrotic Syndrome

Although the cause of idiopathic minimal-change nephrotic syndrome of childhood (INS) remains uncertain, it has been suggested from indirect evidence that this syndrome may represent the clinical expression of a primary immunologic abnormality.

Dr. Robson and his associates have compared serum immunoglobulin concentrations in children with INS with those of children with the nephrotic syndrome secondary to chronic glomerulonephritis (CGN). Results indicate that children with INS may indeed have a primary defect in their immune mechanisms, the observed abnormalities being similar to those described in patients with "x-linked immunodeficiency with increased immunoglobulin M (IgM)."

Throughout the period of this study, the nephrotic syndrome persisted in most CGN children, and this condition was often associated with progressive deterioration of renal function. Serum immunoglobulin (IgG and IgA) levels were significantly reduced in nephrotic patients with either INS or CGN. Although these values increased after treatment of INS with prednisone, mean values remained low. On the other hand, serum IgM concentrations in INS averaged more than twice normal before, during and after successful steroid therapy. Patients with CGN did not have equivalent elevations of serum IgM.

The abnormal pattern of serum immunoglobulin concentrations seen in INS patients -- decreased IgG and IgA and increased IgM -- suggests that the primary defect in INS may not be simple leakage of proteins into the urine (because of abnormally increased glomerular permeability) but may be immunologic, and could consist of deficiency in the thymic-cell function that mediates conversion of IgM synthesis to IgG synthesis. Patients with x-linked immunodeficiency and elevated IgM levels have been found to have thymic aplasia and a similar abnormal serum immunoglobulin pattern.

Lithium Effect on the Kidney

It has been established that long-term lithium therapy is associated with the appearance of a defect in urinary concentrating ability. Neither the rapidity of onset of the lithium-induced defect nor its reversibility following the cessation of lithium administration have been well-defined. Studies by Institute grantee Dr. C. Craig Tisher and his associates at Duke University have attempted to evaluate the immediate and short-term effects of lithium on the urinary concentrating mechanism in vivo, to assess the probable site and spontaneous reversibility of any defect that might be observed, and to evaluate the extent to which any adverse effect of lithium might be prevented or minimized by pre-treatment with amiloride (an agent known to inhibit the epithelial effects of lithium in vitro). The results of this research suggest that alterations in the renal concentrating mechanism can occur rapidly following the onset of lithium administration. They also imply that impaired urinary concentration is due, at least in part, to lithium-induced antagonism to the action of vasopressin on the collecting duct.

Chronic Interstitial Nephritis

The frequency with which various potential causes of chronic interstitial nephritis ("pyelonephritis") are operative is not clearly determined. For example, whether or not bacterial infection ever causes renal insufficiency in the adult, in the absence of other primary causes of interstitial nephritis, is widely debated. NIAMDD grantees Dr. Martin Goldberg and Dr. R. Murray of

the University of Pennsylvania School of Medicine studied 101 patients with interstitial nephritis and have now found that although it is a common form of chronic renal disease, it is rarely caused primarily by infection. Moreover, few patients have "idiopathic" interstitial nephritis, but analgesic abuse (the long-term use of relatively large quantities of acetophenetidin, aspirin, and related drugs) apparently is as common a cause of interstitial nephritis in the United States as it is elsewhere.

The investigators report that interstitial nephritis comprises a significant proportion (33%) of newly diagnosed chronic renal disease, but rarely results primarily from infection. Of interest in connection with the observation that analgesic abuse is not an uncommon cause of interstitial nephritis in the U.S. is that family members other than the patient may also abuse analgesics and suffer from nephropathy. Two of 10 cases in this study had such positive family histories.

Treatment of Renal Stones

In 1973, Institute grantees Dr. Charles Y.C. Pak and Dr. Masahiro Ohata of the University of Texas at Dallas reported that disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP), when added to urine in vitro, inhibits nucleation and crystal growth of brushite, a calcium phosphate salt with a special crystalline configuration which forms the basis for certain renal stones. It had been shown earlier that orally administered EHDP is excreted unaltered in the urine. These findings led to a recent clinical trial of EHDP by the investigators in patients with calcareous renal stones. The researchers have now found that orally administered EHDP inhibits the basic calcium phosphate renal stone formation process without adverse effects and, thus, may have prophylactic value in chronic calcium phosphate stone formers. Except for a transient rise in serum alkaline phosphatase activity and a slight increase in urinary cyclic AMP, no significant side effects were encountered. Intestinal calcium absorption and skeletal bone density did not change significantly. More extensive clinical study and evaluation of its potential toxicity is needed to determine EHDP's ultimate efficacy in the treatment (or prevention of recurrence) of kidney stones.

Urinary Tract Infections

Laboratory and clinical research by Dr. Marvin Forland and associates at the University of Texas at San Antonio has shown the usefulness of the presence of antibody-coated bacteria in the urine as an indicator of the original site of urinary tract infection, often the precurser of kidney disease. These observations have been confirmed independently by others who correlated bacterial antibody-coating with the presence of upper urinary tract infection when using bladder washout techniques.

In further patient studies in Dr. Forland's laboratory, positive bacterial antibody-coating has been found in most patients with chronic pyelonephritis or in patients with acute pyelonephritis, i.e. where there was an active infection in the upper urinary tract, involving one or both kidneys. Twenty-two of their 76 patients who have been followed for up to 27 months to compare their course with the results of sequential examination for bacterial antibody-coating have been found to have persistent infection, relapse or reinfection. These observations showed that there is a persistence of antibody in chronic kidney infection, an absence of antibody in recurrent or persistent cystitis (bladder infection), and the appearance of antibody with invasion of the upper urinary tract (the kidneys).

These investigators have initiated screening studies in a diabetes clinic to investigate the prevalence of urinary tract infection in a diabetic population, to ascertain the incidence of kidney as compared to lower tract (bladder) infection, and to study the relationship of infection to the development of diabetic nephropathy. This patient group will form the core of a long-term study of the applicability of the antibody-coating test in evaluating the efficacy of various therapeutic regimens in urinary tract infections. A collaborative study has been undertaken to evaluate the sequential changes in antibody-coating in women with acute pyelonephritis of pregnancy, who were free of significant bacteriuria on earlier examinations.

Laboratory studies are continuing to define more precisely the correlation of bacterial antibody-coating with urinary levels of specific immunoglobulins, and to ascertain the complement-fixing and opsonic properties of the antibody coating the bacteria.

Diuretics

Furosemide is one of the newer and widely used potent diuretics, whose main action is on the distal convoluted tubule and loop of Henle of the kidney. This drug is usually given to patients with pulmonary edema or edema due to renal failure, and is thought to produce diuresis by inhibiting the action of the sodium-potassium ATPase system. This prevents the reabsorption of sodium in the distal portion of kidney tubules, with a resulting increase in the excretion of sodium and large quantities of water. Recently several reports of transient deafness and one case of permanent deafness have been reported following the use of furosemide. Experimental studies in animals have shown that furosemide produces morphological changes in the stria vascularis of the inner ear.

Grantees of the NIAMDD, Dr. John Najarian and his associates at the University of Minnesota, have reported six cases of permanent deafness encountered in a prospective study of hearing in patients on renal dialysis and transplant patients over a three year period, where in each case, furosemide was being administered at the time of the reported onset of the hearing loss.

In the six cases seen, extensive review of their medical history and drug administration suggested that a period of furosemide administration during impaired or critical renal function was the one factor common to each patient. The onset of deafness was usually insidious and gradually progressive up to six months after the suspected drug administration.

With the experimental evidence that furosemide does induce stria damage and the absence of other recognized causes of deafness in a series of patients, furosemide must be considered the causative agent responsible for the permanent sensorineural hearing loss.

Polycystic Kidney Disease

Polycystic kidney disease (PKD) is an inherited disease whose symptoms are apparent by the fourth decade of life. The disorder progresses relentlessly to chronic renal failure which can be treated only by dialysis or transplantation. Cardiovascular complications, such as hypertension (found in about half of patients with PKD) and stroke, are prominent features of the disorder. It has been estimated that one in 1000 people carry the PKD gene. The last systemic study of this disease was reported in 1957. At the time of these investigations, none of the modern techniques for diagnosis of renal disease, such as excretory urograms with tomography, radioactive isotope scans of the kidney and sophisticated renal function tests, were available.

NIAMDD grantee Dr. Jovan Milutinovic and his associates at the University of Washington are conducting diagnostic tests on patients who may carry the gene for PKD. Since this disease is inherited as an autosomal dominant, 50 percent of the offspring of the affected patients will carry the gene and will ultimately develop the disease. Due to the delayed onset of symptoms of PKD in most patients, the diagnosis is not made until the fourth decade or later. It is anticipated that one or more of the tests in this study will allow earlier detection of PKD carriers. In that case, offspring of affected patients who are not carrying the gene can be relieved of the worry of developing the disease later; on the other hand, those patients who are found to carry the gene can benefit from genetic counselling regarding the advisability of having children as well as from guidance with respect to planning their goals and lifestyles. Early diagnosis will also facilitate better clinical management of the patients, especially with regard to hypertension and kidney infection.

In a pilot study reported by Dr. Milutinovic's group involving twenty offspring of patients with PKD, abnormalities detected by excretory urograms were found to precede more overt evidence of deterioration of kidney function such as decreased urinary concentration capacity, which is probably the first affected kidney function. Renal biopsies in fifteen individuals with negative excretory urograms are being evaluated and correlated.

Evaluation of Research Needs in Nephrology and Urology

Under a contract awarded by NIAMDD, scientists are evaluating the scientific problem areas requiring immediate and long-range future research efforts in the fields of nephrology and urology. These investigators have been engaged to: (1) assess the state of the art in research in these fields; (2) delineate the needs for future basic, clinical, and applied research; (3) evaluate the feasibility of carrying out research in the areas considered significant; (4) consider priorities in approach to the different recommended areas; and (5) produce a detailed working paper resulting from the study, to be distributed to interested scientists and laymen.

ADVANCES IN KIDNEY TRANSPLANTATION

Whereas the NIAMDD has been the principal supporter of research in kidney transplantation, several Institutes of the National Institutes of Health also support research aimed at improving transplantation procedures for various "target" organs. The kidney is the organ most frequently transplanted with tens of thousands of kidney transplantations having been performed throughout the world. Depending on the selection of the donor organ and how close donor and recipient tissue types are matched, between 40 and 80 percent of kidney transplants remain functional after two years. Some recipients who have received a kidney from their identical twin are now in their second decade since receiving a kidney transplant.

Onset of the end-stage syndrome of uremia can be delayed in patients with chronic progressive kidney failure by using special diets. As the condition progresses, however, artificial kidneys become more frequently used and generally enable patients to resume relatively normal lives. Kidney transplantation usually permits the patient to carry on a still more natural life, although he must still receive daily or alternate-day drug treatments to prevent immunologic rejection of the kidney. This chemotherapy must be continued indefinitely in all cases except those involving organ transplants between identical twins. There are frequent complications from continued use of immunosuppressive drugs such as the inability of the body to resist infection in a normal manner.

Research continues to focus on the search for drugs that can suppress the body's immunologic mechanisms, and on improved immunologic matching of donor kidneys with suitable recipients. Transplant rejection is an obstacle to the routine use of kidney transplantation with predictable outcome, and although methods of preserving cadaver kidneys for proper matching with recipients have improved and the problems of preserving kidneys for distant recipients have diminished, improvements are still needed in these areas.

Viral Infection and the Transplant Patient

A large transplantation center operated by Institute grantee Dr. John Najarian and associates at the University of Minnesota screened 132 transplant recipients for viral infections and correlated the clinical course of these patients. One hundred and ten of these patients showed evidence of infection with cytomegalovirus (CMV) uncomplicated by bacterial infections.

The onset of viral infections were almost always accompanied by a significant illness characterized by fever, leukopenia, and renal malfunction. Of 89 patients with cytomegalovirus infections, 83 survived at least three months. Renal biopsies demonstrated typical rejection reactions in all the biopsied patients and renal malfunction usually responded to anti-rejection treatment with corticosteroid or cytotoxic immunosuppressive drugs. Six of the 89 patients with CMV infections died within a month of isolation of the virus.

The investigators found two paradoxical responses to CMV infections in the transplant patients. In the relatively immunocompetent patient, the infection was associated with renal allograft rejection, a prompt antibody response to the virus, and recovery. The severely immunosuppressed patient, on the other hand, cannot make an antibody response and does not exhibit allograft rejection as a cause of renal malfunction. In addition, he may be further immunosuppressed by the viral infection and is susceptible to sequential infections leading to death.

Immunologic Status of Chronic Hemodialysis Patients

The immunologic status of the individual on chronic maintenance hemodialysis is largely unknown. There is a recognized increased incidence of infection in these patients, as well as increased incidence of problems felt to be of infectious etiology. From this information, the question is raised whether, like the patient with renal failure, or the immunosuppressed transplant patient, the patient on hemodialysis is immunologically compromised.

Scientists at the University of Rochester School of Medicine and Dentistry, supported by a contract from the NIAMDD Artificial Kidney Program, recently conducted an evaluation of patients on chronic hemodialysis to assess their immunocompetence. Their findings reveal that the frequency of response of hemodialysis patients to influenza vaccine is identical to that in age-matched normal control subjects and far exceeds the frequency of response of patients with renal failure not on hemodialysis.

The investigators also found that cytomegalovirus (CMV) shedding develops spontaneously in about 15% of older patients on hemodialysis. The antibody development to CMV is no more prominent in this group than in other CMV antibody positive non-shedding individuals. The investigators say their findings indicate that the difference in the way the hemodialysis patient deals

with CMV is not related to the ability to produce antibody, but their findings show that return to hemodialysis and cessation of immunosuppression corrects an immunodeficiency that was present in the transplant recipient, possibly in cell-mediated immunity mechanisms.

The investigators conducted a prospective study of 85 hemodialysis patients which reinforces the evidence that CMV infection has an adverse effect on kidney transplants and may be a major factor in many allograft failures. The investigators found that over half of the hemodialysis patients showed latent CMV infection when tested, but that only 17 percent of the infected patients shed virus while on dialysis and none of them developed clinical illness attributable to viral infection.

Upon transplantation of a kidney from a CMV antibody positive donor to a CMV antibody negative recipient and initiation of immunosuppressive therapy, however, CMV infection was found to be activated, leading to a loss of kidney function, and a significant rise in graft rejections necessitating nephrectomies. The investigators say their study indicates that it is likely the patients acquired the infection at the time of transplantation, perhaps from the donor kidney, and that it is not likely that these infections are disseminated from personnel in the hemodialysis unit or through blood transfusions.

ARTIFICIAL KIDNEY - CHRONIC UREMIA PROGRAM

Advanced kidney failure may be initiated by kidney diseases caused by abnormal immunologic mechanisms, kidney infection, high blood pressure, diabetes, and other systemic diseases, and by congenital abnormalities of the kidney. However it begins, irreversible and potentially fatal kidney failure strikes more than 52,000 patients annually, of which perhaps 10,000 are suitable candidates for maintenance dialysis (or renal transplantation if a matching organ is available).

Patients who do receive dialysis treatment, which continues to be very costly, may experience a number of undesirable complications and must, of course, adjust their lives to the necessity of regular sessions on the kidney machine. Kidney transplantation is a possible alternative, but many patients (especially older ones) cannot withstand major surgery, and even those who do undergo transplantation must be sustained on dialysis until an appropriate donor organ is found. The patient may also need dialysis again if the new kidney is rejected or does not function properly at first. In fact, on the average, approximately one half of transplanted patients return to maintenance dialysis by the end of the third year, post-transplant, because of eventual failure of the grafted organ. Artificial kidneys have other important uses as well: they are used as a means of life-sustaining support in cases of acute kidney failure, and in treatment of moribund patients with accidental or suicidal drug overdosage. In such cases, use of dialysis can be decisive to the outcome.

The Artificial Kidney - Chronic Uremia Program is working to bring about improvements in artificial kidney apparatus and methodologies, to increase their effectiveness, to decrease their initial and operational cost, to improve the rehabilitation of patients treated through dialysis, and to decrease the incidence of long-term clinical complications which may occur in maintenance dialysis. Advancement in all of these areas is still hampered by incomplete knowledge of the basic complexities of the uremic syndrome. Research into the fundamental aspects of the toxic nature of uremia, and basic and clinical

studies into the long-term effects of uremia and chronic intermittent dialysis are critical to the advancement of this important field of investigation and technological development, and are managed and funded by the Institute's Artificial Kidney Program.

At present about 70 research and development projects are supported by contracts with universities, and nonprofit and industrial research laboratories to give a broad approach to these problems of highest priority. The projects are focused on problem areas, including 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 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, and of metabolic wastes and other substances known to accumulate during kidney failure. A large number of research projects are also devoted to the pathophysiology of uremia in an effort to prevent or control complications in patients who have lost their kidney function and are being maintained with the aid of artificial kidneys.

For a decade and a half, dialysis has been used successfully to maintain life in a significant and increasing number of end-stage kidney disease patients (at present -- 22,000). A great deal has been achieved over these years, and clinicians now have an adequate -- though not optimal -- mode of dialysis based on treatment three times each week, each usually lasting six hours. Dialysis therapy, however, is only partially successful in reversing all of the lesions and dysfunctions caused by chronic kidney failure. Patients maintained on dialysis at present exhibit varying degrees of rehabilitation from poor to excellent.

Plans are now under way for the Artificial Kidney - Chronic Uremia Program to conduct a longitudinal nationwide cooperative clinical trial comparing several dialysis therapies on a broader scale and under more controlled conditions than has previously been done. This is necessary because at present there is no reliable, generally accepted body of data to enable physicians to quantify dialysis therapy for particular patients. A primary objective of this study is to develop data which will enable dialysis to be prescribed for the particular circumstances of each patient. In addition, data from the study should permit definition of the lower boundary of dialysis required to maintain patients free of dialysis-induced complications. Another objective is to develop data which will permit definition of the limits within which currently available equipment is capable of shortening dialysis time, thus decreasing the high cost of this treatment, without loss of clinical effectiveness. This new initiative should produce an important body of knowledge upon which the dialysis community of the future can rely, and which would, hopefully, diminish the high cost of maintenance dialysis, for which the Federal Government currently pays out 330 million dollars per year.

Other research and development efforts of the Program are continuing to 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. A high priority for future improvement involves long-term, well-controlled, multiclinic studies to compare the effects of clinical well-being of short-term daily dialysis and long-term periodic dialysis. There is still the need to advance toward a better method of coupling the human circulation to an extracorporeal dialyzing device, as well as to improve the design of the dialyzer itself so as to lower the hours of dialysis from the generally required 18 hours per week to 10 to 12 hours or less.

Scientists in this field must also continue to focus on the prevention of known complications of long-term dialysis, such as bone disease (osteodystrophy), anemia, peripheral nerve damage (neuropathy), and premature cardiovascular death. Particular emphasis is being placed on studies of alterations in patterns of fat and carbohydrate metabolism which occur during the course of long-term dialysis, because these conditions appear to be linked to premature degenerative changes in blood vessels leading to heart disease, the number one cause of death in long-term dialysis, and stroke.

Although morbidity from complications such as osteoporosis, osteomalacia, and hyperparathyroidism have lessened in recent years, many patients maintained with dialysis still 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 of calcium and phosphate from the bone to compensate for low blood calcium levels. Researchers have shown 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. A third factor, related to the uremic patients' inability to utilize vitamin D normally, is discussed below.

Atherosclerosis in Prolonged Maintenance Hemodialysis

The most serious medical problem associated with long-term survival of patients maintained on hemodialysis continues to be the high incidence of atherosclerosis. The evidence today suggests that cardiovascular disease is the leading cause of death among patients undergoing chronic hemodialysis, and is the major factor limiting their survival over the long term.

Dr. Belding H. Scribner and associates at the University of Washington, supported by NIAMDD contract funds, have shown through a retrospective study of 39 patients on prolonged hemodialysis that accelerated atherosclerosis is a major risk. In this study, the incidence of complications such as heart attacks (myocardial infarction), stroke, and refractory congestive heart failure 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 leads to early atherosclerosis and cardiovascular impairment). These patients are exceedingly susceptible to atherosclerosis. The data suggest that the probability of dying from such complications increases with time on dialysis, and that dialysis candidates with existing symptomatic cardiovascular disease should receive a kidney transplant, if at all possible.

Other studies have also shown that death rates of dialysis patients from coronary heart disease are many times higher than in the general population. Since there is no adequate body of knowledge either to explain or solve this situation, continued investigation of this fundamental medical problem is imperative.

New Wearable Artificial Kidney

Scientists at the University of Utah, supported by a contract from the Artificial Kidney Program, have developed a wearable artificial kidney which may be available for general use within a number of years. The seven-pound device will be a welcome and needed addition to the various types of artificial kidneys currently available. The unit can be produced at a considerably lower cost than conventional dialysis machines, and it promises to make dialysis less expensive and possibly less damaging to the patient's red blood cells. It will also provide the great advantage of freedom of movement to users who presently must spend hours connected to large, stationary machines during conventional dialysis treatment.

According to Dr. Robert Stephen of the home dialysis training center at the University of Utah, where the device was developed, a patient using the portable unit would undergo dialysis every day instead of three times weekly, thereby maintaining a more even chemical balance in his blood and tissues and preventing a buildup of waste products. In its present stage of development, the portable artificial kidney cannot remove urea, a major waste product, from the blood. Therefore, in addition to using his portable unit two hours a day while moving about freely, the patient will spend one hour with the unit attached to a stationary 20-liter tank with dialysate (blood-washing solution) to remove urea.

Treatment of Hypocalcemia

Calcium malabsorption in chronic renal disease has been attributed in part to the affected kidneys' inability to convert the vitamin D_3 metabolite--25-hydroxy vitamin D_3--to its most active form--1,25-dihydroxy vitamin D_3. A number of projects supported by the Artificial Kidney Program has shown that the normal conversion of 25-hydroxy vitamin D_3 to 1,25-dihydroxy vitamin D_3 is impaired or absent in dialysis patients since they lack the natural, normally functioning kidney tissue in which this conversion takes place. Moreover, the administration of small quantities of the latter vitamin D metabolite to such patients can bring about a normal intestinal absorption of calcium from the diet, and tends to counteract the frequently developing secondary hyperparathyroidism. Although administration of 1,25-dihydroxy vitamin D_3 has been found to correct calcium malabsorption, it is still expensive and cumbersome to synthesize, making treatment with it on a large scale unfeasible at present.

Thus, attention has been directed to a recently synthesized analog of vitamin D_3--5,6-trans vitamin D_3. In a recent study, NIAMDD grantees Dr. Hector DeLuca of the University of Wisconsin and Dr. Saulo Klahr of Washington University at St. Louis, and their associates, have shown that short-term administration of 5,6-trans D_3 normalizes intestinal calcium absorption in patients with far-advanced renal disease. The researchers believe it may be useful in the treatment of hypocalcemia in patients with renal failure or on maintenance dialysis.

Research Advances Related to Peritoneal Dialysis

Peritoneal dialysis, a method of abstracting impurities from the blood by 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. New approaches to peritoneal dialysis are currently under study which ultimately may result in smaller and more efficient equipment for this mode of treatment, and in less complicated and costly treatment.

Dr. Christopher R. Blagg and associates at the Northwest Kidney Center in Seattle, Washington, have conducted a comparative study of home peritoneal dialysis with home hemodialysis in comparable patients under the care of a community dialysis program. His experience to date has demonstrated that the cost of treatment with home peritoneal dialysis is essentially similar to that of home hemodialysis with reuse of the dialyzer and is lower than hemodialysis if in the latter method the disposable dialyzer is not reused. The rate of hospital-based, emergency back-up dialysis for patients on home peritoneal dialysis is somewhat higher than the rate for home hemodialysis patients, partly because of technical problems with the new automated peritoneal dialysis equipment, and also because, as a result of patient selection, the peritoneal dialysis patients generally tended to have more medical problems. No new major problems or complications with peritoneal dialysis were noted.

Dr. Willem J. Kolff and associates of the University of Utah School of Medicine have developed a sophisticated new access device to the peritoneal cavity. This experimental device permits a continuous flushing of the peritoneal cavity with dialysate (in contrast to the conventional episodic filling and emptying of the abdominal space with a dialysate solution). Preliminary results have shown that this new approach enhances the clearance of creatinine (one of the uremic waste products which must be removed) via the peritoneal route.

Dr. John F. Maher and associates at the University of Connecticut Health Center, and Dr. Karl D. Nolph and associates of the University of Missouri, have obtained preliminary experimental results that indicate that the clearance of some uremic wastes by way of peritoneal dialysis can be improved significantly by the systemic or intraperitoneal administration of certain vaso-active drugs. These studies are based on the assumption that peritoneal clearance may be increased if the blood capillaries which line the peritoneal cavity can be expanded (or possibly even be made more permeable) with the aid of specific drugs generally known to dilate capillaries or to increase their permeability.

Vitamin B_6 Nutrition in Dialysis Patients

The dietary requirement for vitamin B_6 in maintenance dialysis had not been established heretofore; chronic uremic patients have been reported to be deficient in vitamin B_6. Dr. Joel D. Kopple and associates of the University of California, Los Angeles Schools of Medicine and Public Health, have now demonstrated that a majority of patients on maintenance dialysis who ingest the normal amount of approximately 1 mg. per day of vitamin B_6 in food will be deficient in this vitamin. A daily supplementation of 4 mg. of vitamin B_6 corrects this deficiency.

Trace Element Abnormalities

Dr. Allen C. Alfrey and associates of the University of Colorado School of Medicine, have been studying the composition of tissues of maintenance dialysis patients with respect to the concentrations of trace mineral elements which they contain, and have compared these values with concentrations found in normal subjects. They have found a significantly increased concentration of aluminum in the heart, bone, brain, liver, and skeletal muscle of dialysis patients. The most likely source of the increased body burden of aluminum would appear to be the aluminum-containing phosphate-binding gels routinely administered to dialyzed uremic patients since other environmental sources of aluminum have not been identified. Animal studies are in progress to evaluate better the effect of orally administered aluminum-containing phosphate-binding gels on body aluminum burdens. These studies are of particular interest in connection with the possible causation of a dialysis-associated central

nervous system syndrome which leads to a characteristic speech defect, convulsive seizures, dementia and eventually death. Scientists studying this encephalopathy suspect that it might be caused by an abnormal accumulation of some mineral trace element in the brain and thus far the only consistent and most significant abnormality found in such patients is an increased aluminum content of the brain's gray matter.

Protein Requirements of Patients on Maintenance Dialysis

Dr. Frank A. Gotch and associates of the Franklin Hospital in San Francisco have conducted nitrogen balance studies in maintenance dialysis patients who were given diets containing different levels of protein. They have found that patients maintained on a low protein diet which supplies 0.5 gm. protein per kg. body weight were in negative nitrogen balance; thus this intake is not adequate for chronic dialysis patients despite the fact that this level of protein intake is generally considered adequate for normal nutrition in non-uremic individuals. Patients with intermediate protein intakes (1 gm./Kg.), on the other hand, maintain their nitrogen balance. Based on the day-to-day data obtained in these studies, the dialysis process itself apparently increases protein catabolism on the day of dialysis. The reason(s) for this are obscure at present and warrant further investigation.

Blood Cholesterol Levels in Treatment with Oral Sorbents

Dr. Eli A. Friedman and associates of the Downstate Medical Center in Brooklyn, are studying the use of orally administered oxystarch and activated charcoal in reducing the total body burden of uremic waste products. The principle involved is that these waste products will be selectively absorbed and bound to these sorbents in the intestinal tract (to which they migrate by way of the capillaries lining the gut), and will be carried out through fecal elimination. In continuing experiments they have shown that such a treatment decreases the blood-urea-nitrogen level of chronically uremic patients. There is a simultaneous increase in fecal nitrogen excretion during treatment with oxystarch, but only insignificant further increases in fecal nitrogen excretion were noted during combined treatment with oxystarch and charcoal. An interesting serendipitous finding was noted during these studies; mean serum cholesterol fell in the group from 200 mg% to 166 mg% on the average, and in each patient, during combined therapy with oxystarch and charcoal. It was concluded that, in addition to the previously noted increased nitrogen excretion during oxystarch treatment, the reduction in serum cholesterol observed in this oxystarch-and-charcoal trial may have clinical application in uremic and non-uremic patients in connection with future attempts to diminish blood cholesterol levels to retard atheromatous blood vessel degeneration.

Drug Therapy in Renal Failure

Patients with impaired renal function often require major adjustments in dosage of common therapeutic agents to avoid adverse reactions or further renal damage because of reduced or absent renal excretion of these drugs. An exhaustive literature search by NIAMDD grantee Dr. Cecil J. Coggins of Massachusetts General Hospital, Dr. William M. Bennett of the University of Oregon Medical School, and Dr. Irwin Singer of the University of Pennsylvania School of Medicine has now provided a practical guide to pharmacological management of adult patients in this category, particularly those undergoing regular, periodic dialysis.

The researchers have culled from 472 references in the literature what is known about current therapy with commonly used drugs in the presence of renal failure, and compiled a comprehensive guide that can be used to plan treatment more rationally. Drugs are listed in alphabetical order in five tables, either individually by generic name or under subdivisions based on the major type of pharmacologic action. The tables suggest maintenance dosage intervals for common drugs used in patients with renal insufficiency, and are designed to provide the clinician with rough guidelines on which to base safe and effective therapy, but not as a substitute for clinical judgment. The tables will require constant reappraisal to ensure adequate therapy without toxicity, as well as periodic revision to incorporate information about new drugs and newer data about old drugs.

Conferences, Publications, and Scientific Communication

Critical problems and opportunities in kidney disease research are explored regularly through workshops and symposia organized by NIAMDD or co-sponsored with a particular university research center. In 1975, an Institute-sponsored workshop on benign prostatic hyperplasia, or enlargement of the prostate gland, was held at NIH. This disease affects more than 60 percent of the male population over 60 years of age. Twenty-five papers were presented by scientists from Europe, Canada, and the U.S. to 100 representatives of such scientific disciplines as endocrinology, steroid biochemistry, pathology, and urology. A primary goal of this conference was to stimulate interest in this field among investigators and to encourage scientists in various fields to become interested in urological research.

Also in 1975, the Artificial Kidney Program co-sponsored an international symposium on the use of specific chemical binding agents ("sorbents") in kidney failure and selected cases of acute liver failure. The major thrust of this conference which brought together about 150 scientists from the United States and abroad at the Downstate Medical Center, was the use of such sorbents in the direct purification of blood of uremic patients in a process -- hemoperfusion -- in which blood passes directly through a mixture of sorbents which trap and select out of the blood undesirable, toxic waste products. Another major and novel use of sorbents is in dialysis where they are used to regenerate the blood purification solution (dialysate) in artificial kidneys. The proceedings of this conference will be published in the journal KIDNEY INTERNATIONAL to effect a broad dissemination of the latest research findings in this area which is strongly supported by the Institute.

Each year 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 a quarterly 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 popular publication is now being enlarged into a new, comprehensive publication, Kidney Disease and Nephrology Bibliography, a bimonthly which will cover the field of kidney disease and research related to the kidney and urinary tract.

The Institute also distributes pamphlets about kidney disease, dialysis, and kidney transplantation.

Transfer of Data from the National Dialysis Registry

Data gathered by the National Dialysis Registry, organized and maintained by the Institute's Artificial Kidney Program, now covers about 80 percent of the individuals receiving dialysis treatment in the United States. Since its implementation in mid-1969, the Registry has accumulated data on patients treated in approximately 500 dialysis programs throughout the country.

Beginning in April 1976, the collection of the various kinds of data on dialysis patients as well as on patients receiving and donating transplant organs will be assumed by the Medical Information System for End-stage Renal Disease Patients of the Health Services Administration's Bureau of Quality Assurance. The National Dialysis Registry, now being phased out, will transfer its data to that Bureau, as will the NIH-American College of Surgeons Organ Transplant Registry, which previously collected data on organ transplantation under support from a consortium of NIH Institutes.

The National Institute of Allergy and Infectious Diseases Research Effort in Kidney Disease

The National Institute of Allergy and Infectious Diseases (NIAID) focuses research attention on the causes, prevention, and treatment of kidney diseases. The Institute is the focal point for research on the development of ways to minimize rejection of transplanted kidneys. The hope of the future for kidney disease studies lies in a better understanding of allergic, immunologic, and infectious processes. Accordingly, this first report on NIAID's involvement in programs concerned with kidney disease research includes a description of some past discoveries on which current investigations are based.

Glomerulonephritis

A number of studies have increasingly demonstrated the role of the immune system in the disease process leading to glomerulonephritis. Until recently, the cause of this kidney disorder was unknown and only clinical observations suggested an association with preceding infection. We now know that glomerulonephritis is not an infection of the kidney per se but rather results from an untoward side effect of the body's defense mechanism.

In response to the entree of a foreign material (antigen), a highly specific protective substance, antibody, is generated by lymphocytes and plasma cells. As a result of interaction of antigen with specific antibody, aggregates of molecules (complexes) are formed and circulate. Some of these complexes lodge in the kidney's filtering bed (the glomerulus) and incite inflammation within kidney tissue.

Much of this knowledge has come from research carried out by Dr. Frank J. Dixon and his associates at Scripps Clinic and Research Foundation, La Jolla, California, who are supported by a NIAID program project grant. Two major mechanisms responsible for the development of glomerulonephritis have been found: (1) in some cases, antigens from outside the body, such as bacteria and viruses, initiate the process leading to deposition of complexes, and (2) in others, membrane tissue of the kidney becomes altered by disease and actually serves as the inciting antigen.

In the development of an animal model (the rabbit) for the first mechanism, Dr. Dixon has shown that chronic viral infections are important not only for their infectivity per se but also because of the manner in which they participate in the formation of large circulating complexes that deposit in the kidney. When these viral complexes occur during pregnancy, they can in some cases be transmitted to the fetus and deposited in the kidneys.

In the case of the second type, i.e., autoimmune nephritis, the chemical nature of the affected kidney membrane has been described by the Scripps group, thus allowing for appropriate diagnostic procedures.

Since almost 60% of kidney transplants are carried out in glomerulonephritis patients, there has been some concern that failure of the transplanted kidney might be due, not to the immunologic mechanisms of graft rejection but to damage to the kidney by the immunologic mechanisms which led, initially, to glomerulonephritis. To help resolve this question, NIAID has been supporting under contract, the examination by Dr. Dixon and his associates of renal biopsy and/or serum specimens submitted by kidney transplanters.

Since the inception of this contract in 1969, specimens have been submitted for study by 121 institutions on over 4,000 nephritis or transplanted patients. During the past contract year, 524 renal specimens (149 from transplanted kidneys) and 2,075 serum samples from 955 patients were submitted for immunopathologic analysis.

Using immunofluorescent, radioimmune, and antigen or antibody elution and binding techniques, the contractors have been able to screen these specimens and classify many different kidney conditions according to the patterns and types of antibody and immune complexes deposited on the renal tubules and glomeruli. This diagnostic classification has greatly aided attending physicians in making decisions regarding the timing and type of therapy most suitable for an individual patient.

Dr. Dixon's techniques are now being applied in collaborative studies at a number of transplant centers to see whether these immunopathological tests, in the hands of other investigators, can predict end-stage renal disease and graft rejection.

Another advance in understanding glomerulonephritis and other kidney disease has been the demonstration of inflammatory-inducing factors derived from: (1) complement, a normal component of blood, and (2) enzymes contained in normal white blood cells (leukocytes). When the foreign antigen combines with antibody, a cascade of blood components known as the complement system is set into action. Some products of the complement reaction and some derived from breakdown products of leukocytes generate further inflammation and injury within the kidney. At Scripps, Drs. Hans J. Mueller-Eberhardt and Charles G. Cochrane have provided important leads for the development of methods capable of diagnosing and counteracting the injurious effects of complement. For example, an understanding of the mechanism of complex deposition in the kidney filtering membranes has already led Dr. Curtis B. Wilson of Scripps to develop experimental methods, whereby harmful products may be removed by reversing the mechanism of their formation.

At the University of Minnesota, genetic studies have demonstrated that specific hereditary deficiencies of complement components may predispose an individual to the development of glomerulonephritis. Dr. Alfred F. Michael's

laboratory techniques have identified specific components of kidney tissue which, when under the influence of infectious agents or disease processes, can, in turn, result in nephritis. Additionally, studies on long-term circulation of immune complexes have demonstrated that variations in the type of nephritis may be determined by a corresponding variability in the immune response of the individual.

One of the earliest clinical observations of glomerulonephritis was its appearance in association with and/or following streptococcal infections. For this reason, streptococcal products were at first thought to have some special toxic affinity for localization and injury to kidney tissue. Studies of animal models, however, as well as clinical findings, have implicated an immunologic-hypersensitivity mechanism. Evidence now points to the streptococcal product acting as antigen, generating circulating antibody, and resulting in an interaction capable of deposition and injury to the kidney. This has been especially prevalent following streptococcal throat and skin infections, and scarlet fever.

Recent work at the University of Minnesota by Dr. Louis W. Wannemaker has identified the presence of streptococcal antigens and their derivative immune complexes in urine, blood, and kidneys of patients with post-streptococcal glomerulonephritis. Using immunologic techniques, scientists have shown that the tissue proteins excreted by damaged kidney cross-react with streptococcal products. The ability to identify streptococcal products and fractions and the immune response to them is helping to explain the type of bacterial infections requiring control in the prevention of acute glomerulonephritis.

Pyelonephritis

Pyelonephritis, usually caused by bacterial infection of the pelvis of the kidney, has long been of interest to the NIAID. Bacteria in the urine is being investigated by a number of NIAID-supported researchers who are examining the problem of infection caused by a wide array of bacterial agents.

At Stanford University, Dr. Kenneth Vosti has been studying women with urinary tract infections. He has characterized antibodies to urinary pathogens as well as the antigenic makeup of the infecting microorganisms, particularly E. coli strains. A significant rise in certain serum antibodies specific to the infecting organisms was found in acute pyelonephritis, but to a much lesser extent in cystitis. The patterns of the natural history of these infections are beginning to emerge more clearly and could explain why cystitis becomes a chronic problem.

Dr. Lucien Guze at the University of California, Los Angeles, has found evidence that enterococcal pyelonephritis, in a rat model system, may be mediated by an immunologic mechanism. It was also observed that the development of ascending pyelonephritis could be correlated with virulence of the infecting organism. The cell-mediated immune response to the infection is under careful and continuing scrutiny to shed light on mechanisms involved.

Studies on means of preventing pyelonephritis are being conducted at Tulane University by Dr. Gerald Domingue. This investigator is developing a potential candidate vaccine using the common antigen (CA) isolated from certain intestinal bacteria (enterobacteria). He has demonstrated that, in a rabbit model, immunization with specific fractions of the CA from strains of the bacteria created a measurable protective effect against kidney infections following intravenous challenge. Bacteremia in infected animals was also cleared more rapidly in those with increased levels of antibody against the CA antigen.

The evidence thus far that antibodies against the CA of enterobacteria elicit protective activity in experimental pyelonephritis has far-reaching implications. Indeed, isolated and purified CA material may eventually serve as a useful immunizing agent for conferring immunity against pyelonephritis infections.

An intensive study on experimental pyelonephritis by Dr. Abraham Braude is underway at the University of California, San Diego. The ultimate objectives of the study are to prevent kidney damage in pyelonephritis by improving the immune response. Dr. Braude's experimental pyelonephritis model in the rat suggests that the unique characteristics of the interior of the kidney, with its high concentration of sodium, urea and hydrogen ion, result in a condition that can inactivate certain aspects of the immune response to the detriment of the individual.

Urinary Tract Infections

An intense investigation of a substance found in prostatic secretions of normal men may produce results directly applicable to the control of urinary tract infections. Dr. William Fair at Stanford University has identified an antibacterial substance in prostatic secretions of men and in washings obtained from the normal external vagina. This material -- PAF -- has been partially characterized as a low molecular weight protein with a high zinc content. PAF has a pronounced antibacterial effect and it has been found that patients with prostatitis have significantly lower concentrations of zinc in their prostatic secretions. The work done by this investigator and his group is innovative and will undoubtedly lead to a better understanding of the development of urinary tract infections and their relation to bacterial colonization of the genital tract.

The problem of recurrent urinary tract infections in women is the research interest of Dr. Thomas Stamey, also of Stanford University. This urologist has centered his investigation on the problem of bacterial colonization of the vaginal vestibule. He has shown that colonization of the vestibule by intestinal bacteria generally precedes the onset of urinary tract infections. Furthermore, the organisms colonizing the perineal area are frequently identical to those responsible for the subsequent urinary tract infection. In an animal model system, Dr. Stamey has also shown that hysterectomy is associated with a significantly high rate of vaginal colonization. The adherence of the bacteria to cells of the vaginal mucosa may be the key determinant in this type of urinary tract infection.

Wegener's Granulomatosis

For a number of years Drs. Sheldon M. Wolff and Anthony Fauci of NIAID's Laboratory of Clinical Investigations have been studying the largest group of Wegener's granulomatosis patients in the world. The cause of this disease is unknown but it usually involves the kidneys and, untreated, is rapidly fatal.

Over the past several years, the LCI investigators have firmly established a form of drug treatment which produces long-term remissions in Wegener's granulomatosis which can now be considered cures. The drug, cyclophosphamide, is also used to treat malignancies and to prevent rejections of kidney transplants.

Studies by Drs. Fauci, Wolff, and others on the immune response of Wegener's granulomatosis patients and on the effects of immunosuppressive therapy have relevance for the mechanisms of a wide variety of kidney conditions and to the whole question of immunosuppression in man.

In addition, Dr. Fauci, Dr. Wolff and Dr. James E. Balow have successfully demonstrated the feasibility of renal transplantation for Wegener's granulomatosis patients who are in clearcut remission from disease but whose kidney damage before treatment made long-term hemodialysis a necessity.

Other Kidney-related Research

One of the most exciting research findings of the past year was identification by a team of NIAID scientists of a receptor for complement on the glomeruli -- the kidney's filtering bed of blood vessels.

This receptor for complement has been observed in all apparently normal kidney tissue examined. The investigators have not been able to find the specific receptors in patients with immunologic renal disease, indicating that the receptors in these patients have been covered up by immune complexes. In contrast, there was no loss of receptors in patients with nonimmunologic renal disease. This suggests that the receptors for C3b may play an important role in the localization of complexes of antigen-antibody and complement with the attendant inflammation which leads to the renal lesion.

The initial finding of the C3b receptor in the human kidney glomeruli has now been confirmed by 8 other laboratories. The NIAID work was carried out by Dr. Michael Gelfand of Georgetown University Medical Center, a guest worker in NIAID's Laboratory of Immunology; by Dr. Ira Green of the Laboratory of Immunology; and by Dr. Michael M. Frank of NIAID's Laboratory of Clinical Investigations.

At Johns Hopkins University, Dr. William D. Hillis has been concerned with recognition of viral hazards threatening patients with known renal disease. Using immunologic techniques, Dr. Hillis has identified herpes, hepatitis, and cytomegalovirus in end-stage renal disease and found some evidence that these agents -- though not causing kidney disease -- are related to the altered immune state seen in some patients on hemodialysis.

Type B viral hepatitis in hemodialysis centers is a major medical and public health problem. Recent epidemiologic studies indicate that the annual incidence rate of infection is close to 50% in patients and 20% in staff. Family contacts of patients are at increased risk of contracting viral hepatitis. Although available evidence suggests that hyperimmune globulin may be effective in reducing the incidence of infection in patients and staff, repeated inoculations of globulin at 3-4 month intervals may not be desirable.

The NIAID has been actively engaged in developing a hepatitis B vaccine which has been shown to be safe and effective in tests in subhuman primates. Following further testing, the preparation may be made available for clinical trials in the hope that it will eliminate type B hepatitis as a problem in hemodialysis centers.

Other viral infections which are particularly serious in immunosuppressed kidney transplant patients are herpes simplex, varicella zoster, and cytomegalovirus. NIAID is currently supporting collaborative studies of the efficacy of antiviral substances such as interferon and ara-A in the treatment of these infections and results to date are encouraging.

Studies by Dr. Giuseppe A. Andres -- a NIAID grantee -- at SUNY, Buffalo have shown that a type of kidney injury, heretofore thought to be characteristic of organ transplantation, can also occur in patients with kidney diseases. This injury to kidney tubular cells is the result of the development of self-produced antibodies to normal tissue. Furthermore, it has been found that glomerulonephritis due to immune complex deposition can change into an autoimmune process directed against kidney membrane. Dr. Andres' work emphasizes the importance and need to develop effective preventive and treatment measures for adverse immune reactions following infection and serum sickness.

Kidney damage is occasionally seen as an untoward side effect of some medications. In the case of penicillin, Dr. Curtis Wilson of Scripps has shown how the derivative agent, by inducing allergic mechanisms, can result in specific type damage to the kidney interstitial tissue. Direct application of these data to antibiotic treatment of infections can be useful in medical practice.

Interstitial nephritis is recognized as an important clinical entity. Scientists in NIAID's Laboratory of Clinical Investigations are developing a model of this disease in the guinea pig for two specific purposes: 1) to clarify the mechanisms of interstitial nephritis with respect to the body's two immune processes; and 2) to evaluate the efficacy of various immunosuppressive regimens on the disease process.

Studies on the association of nephritis with immunologic consequences of bacterial and viral infections have been extended to parasitic infections. Dr. Robert M. Lewert and colleagues at the University of Chicago, in studying hypersensitivity and resistance in schistosomiasis (a parasitic blood fluke disease), have reported finding antibody-type globulins and complement deposition in kidneys. This finding favors the concept that renal damage in schistosomiasis may be due not to the infecting organism itself but rather to immunologic reactivity, thus offering leads for the development of effective control and treatment measures.

OUTLOOK

Research and development supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases and the National Institute of Allergy and Infectious Diseases continue to be major contributors to the growing knowledge and technology imperative to combating kidney disease. These programs can be expected to advance understanding and initiatives in this field even more decisively following current evaluation of research needs in nephrology and urology. Every effort is being made to insure that the impetus of this vital work in research, prevention, treatment and education is directed and carried through to meet effectively the dire challenges still confronting us. The total program to reduce kidney disease, combined with the highest priority research, should yield maximal benefits in prevention and in lives saved.

HEALTH RESOURCES ADMINISTRATION

Bureau of Health Planning and Resources Development
Kidney Disease and Artificial Kidneys

The development of methods of care delivery to end-stage kidney disease patients has been included in the projects supported by regional medical program grants that were made by Division of Regional Medical Programs (DRMP). These grants are in their final year of support in FY 1976 and are now administered by the Bureau of Health Planning and Resources Development (BHPRD) as a result of the passage of The National Health Planning and Resources Development Act of 1974 (P.L. 93-641). These activities were authorized under the 1970 Amendments to Title IX of the Public Health Service Act which encourages regional cooperative arrangements among health and medical institutions to make available to patients the latest advances in the prevention, diagnosis, treatment and rehabilitation of persons suffering heart disease, cancer, stroke, and kidney disease. By these means, and the promotion of regional linkages to improve care, DRMP has attempted to improve the quality and enhance the capacity of the health care system to provide patient care services.

The development of hemodialysis and transplantation over the past decade as complementary methods of end-stage kidney disease patient care has presented a striking opportunity to organize highly integrated systems of care delivery. The characteristics of finite patient population in end-stage kidney disease, and finite therapies represented by dialysis and transplantation, have given care providers a closed system through which to observe the effects of service patterns altered from traditional health care delivery practices. The objective sought is delivery of high quality care to patients whose illness requires complex and high cost treatment, and for which there has been neither funding nor treatment facilities readily available. The responses to these constraints have indicated increasingly practical methods to deliver lifesaving end-stage kidney disease therapy, and promise to offer useful alternatives in the delivery of other high cost radical medical treatment.

Through developmental and demonstration projects, the performance of hemodialysis in the hospital environment, in low overhead facilities outside the hospital structure, and in the patient's home has proved medically effective.

Collateral developments in techniques of organ harvesting, preservation, and transplantation have made renal homotransplantation a practical method of end-stage kidney therapy. Kidney transplantation is increasingly accepted as preferred therapy for end-stage kidney disease because of its potential for full patient rehabilitation and the opportunity for patient egress from rigorous chronic dialysis treatment.

Experience in the development of these therapies has demonstrated that efficient delivery of dialysis therapy requires concentration of the expensive dialyzers and dialysate delivery systems at central points where medical and allied health personnel can be optimally employed in treating large numbers of patients. Similar centralization of kidney transplantation services is indicated to effectively utilize surgical facilities and the specialized services required to back up radical surgery. Thus, the most effective delivery system of end-stage kidney treatment requires aggregates of hospitals and other health facilities interrelated in an organized manner which assures patient access to high quality care through interdigitation of patient referral, patient registry, alternatives of dialysis and transplantation, organ procurement, laboratory services, specialized health and social services, and continued patient follow-up.

Such a system lends itself to coordinated dialysis-transplantation networks which capitalize on existing facilities, the capabilities of nonphysician personnel, and self-care by the patient. A high proportion of patients accepted into dialysis therapy can be trained to perform this treatment in their homes with the assistance of a family member. Such patients can be treated at a fraction of the cost in chronic in-center dialysis. For instance, a 3-bed dialysis facility which might be dedicated to treatment of six patients a year on a chronic in-center basis can potentially extend treatment to up to 36 patients a year, under present practices, by training the patients to perform self-dialysis in their homes, and can also expand the geographic area which the unit can serve. Limited care dailysis, most appropriately established in dense population areas, permits the extension of dialysis care to patients away from high overhead hospital facilities. Limited care dialysis is particularly appropriate to patients whose socioeconomic status prohibits their treatment in a home environment. In the delivery of transplantation services, economics of numbers can be achieved through centralization which realistically permits populations of 2-4 millions to be effectively served by a central complex of services offered through one or more hospitals.

While selective units perform considerably above the average, nationally, patient mortality averages about 10% per year on dialysis. Average mortality rates after transplantation are higher but the normal life that a successful transplant can provide frequently outweighs the increased mortality risks. In most cases, a patient whose transplant is a failure can be returned to dialysis and be transplanted again at a future time. The two year graft function rate for transplant varies between 45 and 85%, depending on the selection of the donor organ. Evidence suggests that rejections then occur at a rate less than 5% per year. There is considerable regional variation in success rates throughout the country. Implementation of well-developed renal plans, as previously described, shows promise of improving the quality of care being provided in many areas.

The realization of these potentials in the provision of end-stage kidney disease care capability has been the focus of the DRMP kidney disease control activity, and has provided the foundation on which the coverage of end-stage kidney disease treatment has been developed under Title II of the Social Security Act.

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PARKINSON'S DISEASE

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 and Communicative Disorders and Stroke (NINCDS) in 1950.

Obligations for Programs in Parkinson's Disease

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health National Institute of Neurological and Communicative Disorders and Stroke.	$3,342,000	$4,138,000	$5,940,000	$6,096,000	$6,166,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders 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. 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

Advances in the treatment of parkinsonism have been one of the major neurological research success stories of the decade. For the better part of a century, these patients were treated with extracts from the belladonna plant, and, after World War II, a variety of synthetic belladonna-like drugs. These drugs were of some help, but none was truly effective. Then a period of real progress began in the 1950's, when scientists began experimenting with tranquilizers as a means of controlling high blood pressure. This research produced a large amount of new information on the action of chemical neurotransmitters. Contributions came

from a number of countries, but some of the most crucial basic research was done at the National Institutes of Health. It was shown that reserpine, a tranquilizing drug, produces symptoms similar to those of parkinsonism when given in heavy doses. In studying the biochemical effects underlying the symptoms, scientists found that reserpine reduces the high concentrations of the neurotransmitter chemical, dopamine, in parts of the brain responsible for motor control. Then a key finding making these studies (which were primarily aimed at control of blood pressure) relevant to parkinsonism was reported in 1960 when scientists at the University of Vienna found a striking shortage of dopamine in the brains of Parkinson patients at autopsy. This clearly pointed to the possibility of replacement therapy, and led to immediate efforts to treat Parkinson's disease with dopamine.

Early attempts to replace dopamine directly (intravenously) were unsuccessful. It would not cross the blood-brain-barrier--a protective biochemical mechanism which selectively screens substances passing from the blood into the central nervous system. Then scientists found that dopamine's metabolic precursor--the preceding link in the chain of chemical reactions leading to its production--would cross the barrier. The precursor, levodopa, or L-Dopa, at first was not given in large enough dosage, for a long enough time, or by the best route to build up an effective and stable blood level.

Then it was found that by starting patients on small oral doses and increasing the rate very slowly, one could get the majority of them to tolerate effective amounts. After extensive trials in many medical centers, levodopa was approved for prescription sale in June 1970.

The new therapy, however, was not without problems. Chief of these was the side effects caused by the extremely large doses necessary to control parkinsonism 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. In some cases, the side effects were so severe that the drug had to be discontinued. A way was found to reduce the high dose levels--and the side effects--by giving levodopa with an enzyme inhibitor, a substance which slows its metabolic breakdown, allowing more time for it to penetrate, and permitting a reduction in dosage level of around 80 percent. Again after extensive trials, a pill combining levodopa and an inhibitor, alpha methyldopa hydrazine or carbidopa, was approved for prescription sale, and this stands as the most effective antiparkinsonism treatment currently available. The majority of patients are benefited in some degree: some moderately, some with striking relief from their symptoms.

However, in spite of this exciting progress in alleviation of symptoms, the disease progresses, and many patients continue to have severe problems even with the best efforts of their physicians. The obvious need is for an increasingly intense research effort, so that the fundamental causes of parkinsonism can be discovered, the disease process revealed in molecular detail, and a means of halting the progression found.

The Research Program

The NINCDS program in parkinsonism includes grant support for three interdisciplinary research groups at Mount Sinai School of Medicine in New York, Cornell University Medical College, and the University of Colorado School of Medicine in Denver, and approximately 20 smaller, more circumscribed research projects. Also, there is a substantial intramural research program in Bethesda, Maryland. This program has made a very large contribution to the progress described above, and continues to be one of the Nation's major producers of new information in both clinical and basic drug research relating to parkinsonism and other extrapyramidal disorders.

NIH scientists are experimenting with a new approach to treatment of parkinsonism, using substances known as dopamine receptor agonists. These drugs work more directly than levodopa, which must be converted in the brain to dopamine before it can take effect. The scientists have reasoned that one factor contributing to the failure of patients to respond well to treatment with levodopa may be the reduced brain concentration in parkinsonism of the enzyme responsible for converting levodopa to dopamine--L-aromatic amino acid decarboxylase. Another possible source of difficulties is the production of active metabolites of levodopa other than dopamine. For example, norepinephrine may be responsible for some of the unwanted reactions encountered in treating parkinsonism. Both of these drawbacks might in theory be overcome if a drug could be found which entered the brain and selectively activiated dopaminergic receptor sites--a dopamine agonist. Such an agent could still operate when the enzymic machinery required to convert levodopa to dopamine had been destroyed by the underlying pathology of parkinsonism, and if the drug was relatively specific for dopaminergic receptors, adverse effects would not be generated by activation of other synapses.

The NINCDS scientists have recently reported a substantial and statistically significant response in double blind studies with a dopamine receptor agonist, bromocriptine. Adverse reactions were dose dependent, reversible, and qualitatively similar to those encountered with levodopa. In one series of patients, the majority were able to stop levodopa while taking bromocriptine. In another, the drug was added to otherwise optimum therapy, including levodopa. The improvement was measured at about 10 percent in patients with minor disabilities, and about 20 percent in those with more severe disease.

The Mount Sinai School of Medicine in New York is the site of the largest interdisciplinary research team supported by a grant from the Institute. This group, now in its 13th year, has made major contributions to drug therapy in parkinsonism, and also has served as a leading training center for young scientists interested in this field. During this time, it has operated a clinical center for Parkinson patients, and has conducted hundreds of basic studies in virtually all areas relevant to parkinsonism, including neurochemistry and pharmacology, neurophysiology, ultrastructure, and histochemistry, nerve regeneration, and neurovirology.

At present, clinical studies include a long-term effort to determine the effect of levodopa on life expectancy, studies of several untried drugs on disorders different from but similar to parkinsonism, and studies of the "on-off" effect--an abrupt change from akinesia (inability to move) to normal function and then back again, which many patients on levodopa experience. Also in progress are studies aimed at measuring intellectual deterioration in parkinsonism, and at determining whether levodopa affects the process. In a report published this year, the Center noted a reduced ability in patients to form concepts, and no apparent benefit from the drug in concept formation. However, the scientists did find an improvement in "vigilance" with levodopa.

Other clinical studies at the Center related to eye movements in parkinsonism as a possible diagnostic aid and means of evaluating the disease state and therapy; the question of whether the dopamine deficiency of parkinsonism also exists in the retina; and studies of the effect of levodopa on carbohydrate metabolism.

The Center has a bank of brains removed at autopsy, and is continuously adding to it. The brains received are from patients who have been thoroughly studied clinically, and samples of tissue are made available to researchers. This is an unusually valuable research resource.

Several examples of the basic research projects at the Center are studies of two newly discovered proteins in nerve cells which may be part of the mechanism of transmitter release; a long-range study of the exact neuronal morphology, synaptology, and anatomy of the basal ganglia--the brain area most affected in Parkinson's disease; and studies of viral infection of nervous tissue. Objectives of the latter project are to study the nature of viral latency, the sites, time course and development of herpes simplex virus infection in animals, and the biochemistry of experimental viral encephalitis.

At Cornell University Medical College, the group credited with the original development of levodopa therapy is continuing an extensive biochemical and genetic exploration of parkinsonism. First interested in manganese poisoning, whose symptoms are similar to those of parkinsonism the Cornell scientists are continuing studies of the role of manganese in neurotransmission.

By feeding manganese to newborn mice, they have found that cerebral dopamine levels correspond with cerebral manganese. They feel that this provides strong evidence that trace quantities of the metal participate in the development and normal functioning of the dopamine neurochemical system.

Also being conducted by this group are studies of a number of novel anti-parkinson drugs. One of particular interest is N-propyl norapomorphine, or NPA. An analogue, or close relative of the drug, tried earlier had caused azotemia (urea in the blood) and had to be abandoned; NPA, however, completely circumvents this problem, and appears to have other advantages over prolonged levodopa administration, particularly in that it reduces involuntary movements and the "on-off" phenomenon mentioned above. Combined with small doses of levodopa in the form of Sinemet, the scientists found it superior to other treatments in that it offers maximum antiparkinson effects, maximal diurnal stability of symptoms, and minimal dyskinesia (involuntary movements).

An interesting drug development reported by the Cornell workers during the year concerns diphenylhydantoin (DPH), an anticonvulsant drug widely used in medical practice, and of considerable current interest in clinical research. Whereas it has reportedly improved the symptoms of otherwise untreated Parkinson patients, it was found to block the therapeutic effects of levodopa, both in Parkinson patients and in patients with manganese poisoning. Thinking its use might throw light on the puzzling fact that symptoms of Parkinson's disease and Huntington's chorea are affected in opposite directions by some tranquilizers and levodopa, the scientists tried DPH in Huntington's chorea, but found that here the reciprocity did not exist: the patients were made worse.

In a study of long-term experience with levodopa, the Cornell scientists have followed one group of 67 patients very closely for up to 8 years. They have found that 10 percent of the patients continue to improve after the first year of treatment; that 60 percent retain the initial improvement for 2 to 7 years, and that in 30 percent some loss of therapeutic effect or emergence of limiting side effects becomes evident after the first year.

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 antiparkinsonism drug yet found, studies of neurotransmitters in parkinsonism could lead to new ways of treating one of the most baffling of the mental disorders.

This year the Denver scientists reported success in treating the light-headedness and frequent fainting some patients experience when on levodopa. They found fludrocortisone to be effective and safe, and a welcome alternative to reducing the levodopa dosage to less than ideal levels.

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, NINCDS 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. 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.

SICKLE CELL DISEASE

Sickle cell anemia is a hereditary disorder characterized by the presence of painful "crises," a chronic anemia, related to accelerated destruction of red blood cells, and acute or chronic damage to various organs. All these clinical manifestations are due to the presence of an abnormal hemoglobin (HbS) which aggregates within the deoxygenated red blood cells, leading to a crescentic "sickle" shape of the cell known as the "sickling phenomenon." 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 five hundred. It is estimated that some 40,000 to 50,000 black persons are affected.

Sickle cell trait is the carrier state wherein an individual has genes for both sickle hemoglobin and normal hemoglobin. Rarely are there significant clinical problems associated with the trait. 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. Treatment, however, is being constantly improved. This includes analgesics, fluids, blood transfusions, proper nutrition, good hygiene, bed rest, and protection against acute infections and other stressful factors that contribute to crises.

The Department of Health, Education, and Welfare's (DHEW) activities relating to sickle cell disease are centered in the National Institutes of Health (NIH) and in the Health Services Administration (HSA). The NIH serves as the lead agency for the coordination of the overall national sickle cell program. Funds for the program are part of the budget of the National Heart and Lung Institute. The NIH's research activities in sickle cell disease are primarily the responsibility of the National Heart and Lung Institute. The National Institute 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 the Sickle Cell Disease Office in the Bureau of Community Health Services.

Obligations for Programs in Sickle Cell Disease

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health:					
National Heart and Lung Institute	$15,824,000	$16,010,000	$16,791,000	$18,031,000	$17,930,000
National Institute of Arthritis, Metabolism, and Digestive Diseases	1,120,000	1,335,000	1,070,000	1,016,000	482,000
National Institute of General Medical Sciences	100,000	100,000	100,000	100,000	100,000
Total	$17,044,000	17,445,000	17,546,000	19,047,000	18,512,000

HISTORICAL BACKGROUND

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 amount was later increased to a level of $16 million in FY 76.

Subsequent to the President's initiative, the Secretary of DHEW established the National Sickle Cell Disease Advisory Committee, which recommended that the earmarked funds for the National Sickle Cell Disease Program (NSCDP) be divided between research and demonstration activities.

The objectives of the NSCDP as further recommended by the Advisory Committee are: to decrease the morbidity and mortality from sickle cell anemia through research and development, both at the fundamental and clinical level; to initiate and expand community education, screening and counseling; to educate medical and allied health professions; to broaden monetary support through federal, state, local and non-government participation; to strengthen and expand the base of black professional and technical personnel; and to improve clinical care for patients.

A program was developed to implement these goals and objectives. Sickle cell activities for the NSCDP are carried out by the National Institutes of Health and the Health Services Administration. The chief, Sickle Cell Disease Branch, Division of Blood Diseases and Resources (DBDR), National Heart and Lung Institute (NHLI), NIH, is the Coordinator for the National Sickle Cell Disease Program.

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 40,000 to 50,000 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, DBDR, NHLI, in cooperation with the Sickle Cell Disease Office, Bureau of Community Health Services, HSA, and the Hematology Section, Center for Disease Control (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.

Authorities under the National Sickle Cell Anemia Control Act expired June 30, 1975.

NATIONAL INSTITUTES OF HEALTH

National Heart and Lung Institute

COMPREHENSIVE SICKLE CELL CENTERS

Comprehensive sickle cell centers administered by the Sickle Cell Disease Branch, Division of Blood Diseases and Resources, NHLI, bring together research (basic, clinical, clinical trials, clinical application, research training) and community demonstration service (education, hemoglobin diagnosis and counseling). These centers concentrate resources, facilities, and manpower in a coordinated approach to solving the multiplicity of problems related to sickle cell disease, bridge the gap between scientific investigations and service efforts, and bring findings in one area into practical use in others. In this manner, research findings are most efficiently made available for incorporation into the health care delivery system.

Fifteen (15) centers have been established in geographic areas serving large populations at risk for sickle cell disease. Of the funds available to these Centers, approximately one-third is devoted to research investigations and two-thirds to service and demonstration programs. Research findings have documented the severe socio-economic impact of sickle cell disease not only on the patient but also on involved families and communities. Increased maternal and infant mortality have been attributed to this disease. Early diagnosis, however, coupled with improved prenatal obstetric care regimens developed in the Centers has significantly reduced such mortality. Demographic features and prognostic indices have been developed to serve as a predictive aid in reducing frequency and severity of painful symptoms to patients with sickle cell anemia.

Studies of emergency room procedures for patients with sickle cell crises have resulted in improvement of such treatment and earlier alleviation of pain and the sequelae of crises. Because of the systemic nature of sickle cell anemia, every tissue and organ in the body is subject to the effects of this disease. To document and possibly reduce the extent of this damage, studies are being conducted in the centers on all the major organ systems (i.e. opthalmological effects, neurophysiological studies, bone lesions, kidney, liver, heart, lung, growth and maturation, etc.). Correlation of information from these investigations is in progress to clarify the normal course of sickle cell anemia and the many variables that contribute to the broad spectrum of severity observed in different patients. Investigations in progress on the blood flow, rheology and coagulation in sickle cell anemia have yielded valuable understanding of mechanisms involved and point hopefully to palliative measures for the treatment of patients. The search for compounds that might reduce or prevent the sickling of affected red blood cells continues. Carefully controlled studies with animals have led to improvement and refinement of instrumentation, operative procedures, and hemoglobin identification techniques which are promising for the midtrimester prenatal diagnosis of fetal hemoglobin patterns.

The education programs being conducted in the comprehensive sickle cell centers have proved highly effective through a wide range of specialized educational materials, exhibits, seminars, and lectures directed toward increasing the awareness and knowledge of the general public, high school students, medical students, interns, residents, and practicing physicians with special attention to socio-economic and ethnic considerations.

All centers participate 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 and contributed to the overall field of scientific information relating to hemoglobinopathies.

Counseling programs within the centers have been developed to provide effective commmunication with individuals through the use of illustrations and discussion techniques. 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 the combination of sickle hemoglobin and with other abnormal hemoglobins. Counseling is of a non-directive nature and is in effect a continuation of the educational process provided to the individual before testing.

During these sessions, accurate definitive information related to the specific case is provided to the individual and assistance is given in the interpretation of this information. Decisions regarding this information, however, must be made by the individual without direction or influence, even of a covert nature, by the counselor. This procedure results in a high degree of acceptability of these programs 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 Bureau of Community Health Services in the Health Services Administration currently with support from NHLI. This service component supported twenty-four (24) sickle cell clinics throughout the country in FY 76. The clinics are established to determine methods of carrying out service activities such as public awareness, education, screening and counseling. These activities are provided in various settings and through health departments, school systems, neighborhood health centers, hospitals and free-standing clinics. Also, the clinics are closely linked to other community activities and often provide a point of entry for individuals into comprehensive health care systems.

During the past year, this program component initiated the development of education and counseling protocols to assure content accuracy and uniformity in all clinics. It is anticipated that the clinics will serve as a model that will enable replication by non-federal programs that provide sickle cell services.

Reporting requirements are utilized by all the screening and education clinics whereby types and quality of program services can be monitored. To date, screening services have been utilized by over six-hundred thousand individuals and information has been provided through these clinics to over four million people. There is a constant demand for quality services through the clinics in most of the communities "at risk" in this country.

MISSION-ORIENTED RESEARCH AND DEVELOPMENT PROGRAM

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 impeded or prevented, perhaps by a suitably designed pharmacologic agent, both the quality and duration of life of patients with sickle cell disease would be markedly improved. Sixteen contracts were supported in FY 76 to study the molecular, cellular, and clinical manifestations of sickling.

Presently, it appears unlikely that cyanate may be useable therapeutically by the oral route because of its toxic effects. But new approaches are actively under study in order to understand better the mechanism of drug action. Studies are still in progress to evaluate the use of cyanate, administered extracorporeally.

Notable accomplishments during the past year include the development of techniques for the separation of fetal and adult hemoglobin and the study of the synthesis of HbA, HbS and HbC. Also, adult hemoglobin synthesis has been studied in a large range of fetuses from six weeks onwards, and a guide has been developed for the normal range through gestation. These data are significant because they may form the basis for clinical diagnosis of sickling conditions in fetuses.

A workshop was held in September 1975, to discuss the development of extracorporeal techniques for treatment of sickle cell blood employing cyanate as a possible therapeutic agent. A consensus was that a continuous flow technique for treating blood extracorporeally should be developed.

Valuable information has been provided about the neonatal and early childhood of sickle cell disease patients. Recent studies have identified newborn infants, using acid elution agar gel hemoglobin electrophoresis. These afflicted infants are being observed in clinics and their homes for the purpose of defining the clinical course of the disease. Other studies have successfully identified the point of onset of functional asplenia in the patients studied and have proved that this defect is acquired rather than congenital.

In addition, it is now possible to correlate these findings with the observed decrease in fetal hemoglobin to levels below 20 percent, which occurs in most sickle cell infants at variable periods. These observations point to the need for research to study the mechanisms of gene activation.

On December 10, 1975, more than 30 leading scientists in the area of sickle cell research convened at a one-day symposium in Dallas, Texas, to discuss the most recent advances on the molecular and cellular aspects of sickle cell disease. It was evident at the meeting that the focus has improved, and that much more pertinent information is available, even though much remains to be more clearly defined. Several important observations were presented about gross structure of polymers of hemoglobins. A consequence of these presentations will be the provision of basics for the design of effective anti-sickling agents in the treatment of sickle cell disease.

BIOMEDICAL RESEARCH PROGRAM

A program of investigator-initiated research is being conducted by the Division of Blood Diseases and Resources, NHLI. Forty-nine grants are presently being supported by the Institute. These investigations include studies of the basic structure of sickle hemoglobins, methods of altering the abnormal structure, the synthesis of hemoglobin, 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 disease 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 contributions by psychologists and social workers.

To broaden the approach, a contract was awarded in FY 76 to three (3) non-governmental organizations to carry out programs in public awareness, to aid in the dissemination of factual information, and to conduct educational programs in sickle cell throughout the country. The contract program is aimed at health providers, employers, insurance companies, health educators, and persons who have sickle cell anemia or sickle cell trait.

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 (CDC) trains personnel of federally-funded sickle cell projects 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 screening projects. Laboratory personnel have also increased their knowledge through the hemoglobinopathy workshops conducted by CDC.

RELATED ACTIVITIES OF OTHER NIH INSTITUTES

The National Institute of Arthritis, Metabolism, and Digestive Diseases is supporting several projects directed towards diagnosis of sickle cell anemia in utero to assist early diagnosis in the fetus. Since sickle hemoglobin is expressed primarily in the adult and the chromosome carrying the gene has not been identified, current methods cannot detect the disease in utero. Research sponsored by the National Institute of Arthritis, Metabolism, and Digestive Diseases has identified markers on the likely chromosome in several related individuals that make it possible to identify the sickle gene. An alternate approach is to obtain cells from fetal blood vessels, culture them, and attempt to detect any sickle hemoglobin they produce. This technique has recently been successful for a related hemoglobinopathy, thalassemia. Work is proceeding to adapt it to sickle cell anemia.

The National Institute of General Medical Sciences is continuing to support 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. Several other studies are concerned with the evaluation of genetic counseling procedures and of the extra-corporeal administration of sodium cyanate therapy in sickle cell disease.

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 76 at a total funding level of approximately one million dollars.

SPINAL CORD INJURY

For the unfortunate victim, severe spinal cord injury is far more than an acute disorder. If his spinal cord is severed or if the fiber tracts within it are anatomically interrupted, he is left without higher central nervous system control of function below the lesion and the resulting effects are staggering. In cases of complete cord transection, paraplegia or quadriplegia occurs immediately and is permanent, since effective regeneration within the central nervous system does not take place. Suddenly, the patient is locked in a motionless, unfeeling body, forever dependent upon others for help in performing bodily functions and daily tasks. Although continuing advances in medical care and rehabilitation make it possible for increasing numbers of the spinal cord injured to lead useful, productive lives, most will always have special medical and surgical problems.

The National Paraplegia Foundation, a voluntary health agency, estimates that 100,000 Americans suffer from spinal cord injury. The Foundation indicates that there are approximately 7,500 new injuries each year which result in paraplegia as a result of automobile or motorcycle accidents, falls, sporting and industrial accidents, and gunshot wounds. Ninety percent of the victims are between the ages of 16 and 30.

It is estimated that the cost of immediate and lifetime care of a paraplegic ranges from $50,000 to $250,000. If the victim is not treated at a specialized center these costs can double or triple. Insurance is usually inadequate, so the victim and his family, or the community must bear the bulk of these costs. 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 $2 billion a year in the U.S. alone. In terms of personal tragedy, the toll is immeasurable.

The Department of Health, Education, and Welfare's responsibility for research programs in spinal cord injury is centered in the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the National Institutes of Health; for rehabilitation, the Rehabilitation Services Administration; and for service, the Health Services Administration.

Obligations for Programs in Spinal Cord Injury

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health:					
National Institute of Neurological and Communicative Disorders and Stroke	$5,613,000	$6,309,000	$7,673,000	$7,882,000	$7,941,000
Office of Human Development:					
Rehabilitation Services Administration	2,789,000	2,816,000	2,810,000	3,850,000	3,604,000
Total	8,402,000	9,125,000	10,483,000	11,732,000	11,545,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders and Stroke

The human spinal cord is a bundle of nerve fibers and cells measuring an average 17 inches in length. It provides the central connections between the brain and the muscles, skin, and internal organs, and is securely encased by bony vertebrae. These circular blocklike bones allow a remarkable range of motion while normally protecting the spinal cord and nerve roots. Nevertheless, injury to the nervous system can and does occur.

A spinal cord injury causes an interruption of the nerve messages that are transmitted from the brain down to the cells which originate movement and from the skin and muscles to the brain. Such an injury may be compared to a cut in a telephone line which causes a sudden failure of incoming and outgoing messages. Although the circuits above and below the level of the injury may be completely alive, messages can no longer travel to them. Thus, when the spinal cord is irreparably damaged, the victim experiences lack of all sensation and all voluntary movement below the level of the injury.

Causes of Spinal Cord Injury

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 cause most of the direct injuries to the spine. Fractures, however, have long range serious consequences mostly 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.

More frequently, however, trauma occurs from indirect injury to the spinal cord. This may result from 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 jackknifed 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 seizures.

Types of Spinal Cord Injury

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). These injuries result primarily 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 the cord's substance, and (4) compression of the cord's blood vessel supply.

Severity of Spinal Cord Injury

Because the central part of the spinal cord is soft and easily bruised or squeezed by pressure from surrounding bones, cord damage can and does occur above or below the level of bone injury. 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 prognosis because more of the cord remains functional. Once the spinal shock wears off, muscles controlled by nerves from the spinal cord above the injury often regain full function.

Injury in the upper cervical cord is the most life-threatening of all because of the frequent development of respiratory paralysis. Lesions below the fifth cervical vertebra are less grave 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.

Another key factor in predicting recovery is the extent of cord injury. A cord that has been completely severed by a bullet or a penetrating missile fragment cannot be repaired, and such an injury always results in permanent motor paralysis and sensory loss below the level of transection.

Some degree of improvement is to be expected in all survivors of spinal cord injuries except those cases of cord transection. 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

During World War I only 10 percent of paraplegics lived for a year following injury. Today 90 percent survive, and after the first year their mortality rate only slightly exceeds that of the general population. These excellent results are attributable to a number of factors ranging from the advent of sulfonamides and antibiotics to the recognition of the value of the comprehensive approach to the problem of spinal cord injury. Indeed, the cooperation of neurologists, neurosurgeons, neuroradiologists, psychiatrists, orthopedists, reconstructive surgeons, psychologists, and allied health professionals in the evaluation of each patient at every stage of treatment and rehabilitation is almost revolutionary. An earlier despairing attitude has given way to hope of orienting the patient to a new lifestyle and helping him back to an adjusted, productive life.

Sophisticated mechanical aids assist in the return to normalcy. Aids include a pneumatic brace which assists some patients in walking; improved devices for operating automobiles; a rocking platform that can be used by a wheelchair patient to relieve constant pressure on the body and consequent skin breakdown; the prototype of a voice-controlled wheelchair which responds to five different commands; and a modification to a standard computer terminal that allows a physically handicapped person who is unable to write or type to communicate with a computer.

Spinal Cord Injury Research Program

The NINCDS conducts and supports a long range comprehensive spinal cord injury research program which has four major thrusts: (1) development of quicker and better methods of treating patients whose spinal cords are not completely severed; (2) application of recent advances in the basic neurosciences, engineering, and physical sciences to the development of prostheses for paralyzed patients; (3) the use of arteriography, new non-invasive scanning techniques, and evoked responses in diagnosing and monitoring spinal cord injury; and (4) research on regeneration of the spinal cord.

New Approaches to Acute Injury

In most cases of spinal trauma, the cord is not cut in two; rather it is bruised. Immediately after injury it appears swollen, but in a matter of hours hemorrhage into the cord takes place, causing the cord to degenerate until there is nothing left at the level of the injury. For the patient, the result is the same as if the cord had been severed--permanent paralysis.

Over the past few years, there has been experimental evidence from a number of laboratories suggesting that in some cases like this the process whereby spinal injury leads to paralysis might be arrested. This possibility is being extensively explored in Institute-supported 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.

Research at these centers have both "basic" and "clinical" aspects which frequently overlap and interlock. Thus, potentially useful methods of treating spinal cord injury are tested for effectiveness and safety in the laboratory before being used on patients. The centers also have a potential population of well studied cases treated conventionally as a control series.

Basic research at all of the Centers is focused mainly on the complex problems of the biomechanics of injury and on the chain of chemical and physiological events leading to cord deterioration.

As stated earlier, the spinal cord is rarely damaged directly. Instead, injury occurs most often from twisting, flexion, or extension. Consequently models which approximate these forces are needed for studying their affects on the cord. One new instrument which was developed recently delivers a calibrated injury force to the cord of the experimental model. This force can be displayed on an oscilloscope as a curve and photographed. In principle, a strain gauge is used to measure the force delivered to the cord. This work was done by Dr. Phanor L. Perot, Jr. at the Medical University of South Carolina Center.

The sequence of events following severe cord compression is believed to be (1) conduction block of axonal transmission, (2) change in vascular flow accompanied by edema and hemorrhage, (3) cellular response to damaged tissue, and (4) development of scar tissue and abortive axonal regeneration.

In experimental models of spinal cord injury, attempts are being made to pinpoint what happens, and when, and to test ways to intervene and interrupt the chain of events. Generally, scientists are studying the action of pharmacologic agents, local cooling, surgery, and steroids on the traumatized cord in the search for a therapy that will preserve or restore function.

At the Ohio State University Center, Dr. William E. Hunt, in blood flow studies of spinal cord injury, showed immediate major shifts in blood volume and changes in the blood-spinal cord barrier. However, the fact that the ensuing structural changes in vessels, while rapid, were progressive, suggests that pharmacologic or other measures might be found to arrest that progression.

In a number of laboratories, studies have been carried out on the changes in the level of norepinephrine in the injured segment of the spinal column at varying intervals following injury and following the application of varying degrees of force. These studies have failed to confirm the hypothesis that the catecholamine, norepinephrine, has significance in producing constriction of blood vessels in the spinal cord. Recently, an investigation by Dr. Collins at the Yale Center led to the observation that following spinal cord trauma there is a change in catecholamine synthesis which may explain some of the changes in the level of catecholamine associated with spinal injury.

Although these and other basic studies at the Centers have not yet produced breakthroughs which may be applied clinically, they are continuing to produce vital new knowledge about the injury process, are stimulating research in other laboratories, and are promoting a healthy exchange of information about acute spinal cord injury among investigators and clinicians in this country and abroad.

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There have been a number of clinically useful developments coming out of the research centers during their two full years of operation. For example, results of electrophysiological studies conducted by Dr. Phanor L. Perot, Jr., at the Medical University of South Carolina Center have shown for the first time that there is excellent correlation of evoked potential measurement with the clinical state of the patient. By repeatedly stimulating a peripheral sensory nerve with a mild electrical shock, it is possible to record from the scalp a response which provides valuable information about the functional integrity of anatomical pathways in the spinal cord. This technique is ideally applicable to the patient with spinal cord injury where the first and most important question to be answered is whether the cord has been transected, or if some neural activity can still be conducted through the damaged area.

At the New York University Center, handling techniques have been developed for use by rescue squads, police, and firemen at the accident site. Dr. Joseph Ransohoff is the Director of this Center. These methods are making it possible to transport the patient in such a way that the spine is immobilized without being manipulated, at least until the time the nature of the injury is known and any necessary manipulation can be carried out by well informed, skillful physicians.

Last year at this Center, Dr. Ransohoff completed the development of a Spinal Cord Intensive Care Unit within its facility. Activities there are directed towards increasing the referral network of hospitals in order to increase the number of patients available for intensive investigation in the unit within the first few hours after injury, and for the precise measurement of rapid changes in the patient's condition. Thus medical or surgical intervention can be initiated even before clinical symptoms indicate that a noxious change in the patient's condition is occurring.

Investigators at the Phoenix Center have developed and put into use a new cervical-thoracic immobilization device to minimize the additional cord damage which might occur in transit. The Director of this Center is Dr. Eduardo Eidelberg.

These and other techniques, devices, and equipment are an outgrowth of the Center's program 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 early phases following injury may well prevent permanent paralysis in the patient.

Radical changes in techniques for removing bone fragments are among the important surgical developments at the Centers. Not only is the pressure on the spinal cord from these fragments excruciatingly painful, it can also be a direct cause of cord damage and paralysis.

Within the Centers measures are being sought to prevent, modify, or minimize the development of "pressure sores" in the spinal cord of an injured patient. Open granulating wounds have now been produced experimentally and scientists are assessing the value of treating them by enzymes, topical antibacterials, biologic dressings, and systemic antibiotics.

Gradually the NINCDS Centers are becoming complementary to the Regional Centers which are operated by the Rehabilitation Services Administration for the treatment and rehabilitation of patients with spinal cord injuries. More and more, methods developed and tested at the Institute-supported facilities are being demonstrated for clinical use at the regional level.

The NINCDS continues to maintain liaison with the Veteran's Administration with the intent of developing mutually beneficial opportunities for research on spinal cord injury. The Institute also expects to obtain valuable data which may serve as a basis for future research from the National Spinal Cord Injury Registry. The Registry, established by the Department of Defense at the Medical University of South Carolina, is currently analyzing information which has been recorded on hundreds of spinal cord injured patients, including those from the NINCDS Centers.

In addition to its Centers, the NINCDS also supports a large program project at the University of North Carolina, Chapel Hill, where multidisciplinary basic research on acute spinal cord injury is being pursued, as well as a program of targeted research grants on the problem of acute spinal cord injury.

Neural Prostheses Program

Usually the muscles of paraplegics are intact following injury to the spinal cord. Through its research contracts program, the NINCDS is investigating how to activate these muscles in a coordinated manner with electrical signals derived from the muscles of the unparalyzed part of the body.

Utilizing this so called "by-pass" approach, Dr. Thomas J. Mortimer and Dr. Hunter Peckham at Case Western Reserve University, have been able to activate both paralyzed flexor and extensor muscles in the hand of a quadriplegic patient, and to accomplish this with less "hardware" than had been necessary in earlier experiments. Using this prosthetic device the patient can grasp small articles such as pencils and chessmen or raise a paper cup of water to his lips.

Another promising NINCDS contract concerns a new approach to the development of a prosthetic device for bladder control, a grievous problem in paraplegia. Dr. Emil Tanagho of the University of California, San Francisco, has found that dogs who have lost bladder control because of severed spinal cords can be caused to empty their bladders by electrical stimulation of the sacral spinal nerve roots below the level of the cord transection. Such stimulation causes contraction of the bladder wall with minimal or no sphincter contraction--a major advance. It is hoped that further animal studies will permit the technique to be extended for use in humans with neurogenic bladders.

Angiography As a Diagnostic Tool

Angiography is the process of taking X-ray pictures of blood vessels after first injecting a radiopaque substance. Since 1964, NINCDS neuroradiologists have used this process in studies of the spinal cord and have developed it into a reliable diagnostic tool.

In this year's studies of patients with paraplegia, direct radiographic magnification was found useful. The most impressive finding has been the discrepancy between the gross bony-ligamentous damage and the relative sparing of the vascular system. It is considered remarkable that in cases of posttraumatic paraplegia and massive skeletal-ligamentous injuries, the continuity of the vascular pathways (at least the large vascular channels) may be intact.

The NINCDS neuroradiologists have attained three "firsts" in these studies. They have demonstrated, by high magnification, the blood vessels inside the spinal cord. In another case, overflowing of contrast medium into the epidural space was shown, indicating "ongoing" bleeding. In the case of a quadriplegic patient studied by angiography who had died several weeks later, the investigators succeeded in obtaining a microangiographic cord study and were able to compare angiography of the cord in the living body and postmortem microangiography of the cord.

In order to expand the clinical application of arteriography of the spinal cord, NINCDS radiologists are also working with experimental angiographic and microangiographic models in primates.

Computerized Axial Tomography

Computerized axial tomography, a revolutionary new radiographic technique which permits cerebral pictorial analysis, for the first time can now be applied to other parts of the body as well.

A modified X-ray scanner, the Automatic Computerized Transverse Axial Scanner (ACTA-Scanner), which was developed at Georgetown University and first used there in February 1974, is able to scan soft tissues everywhere in the body, including the cervical spine and cervical cord.

NINCDS neuroradiologists have played a central role in the utilization of the ACTA-Scanner. In scans of patients with syringomyelia and hydromyelia, the fluid filled cavities associated with these disorders were disclosed in several instances as low-density foci on the cord. It is anticipated that the scans may be helpful in the assessment of certain aspects of acute spinal cord injury, associated bleedings, and delayed cavity formation.

Nerve Growth and Regeneration

If the problem of functional regeneration within the central nervous system could be solved, it undoubtedly would be heralded as the most important single advance in the history of neuroscience, if not in all of biomedical research.

Not only might the ability to induce regeneration of severed nerve fibers in the spinal cord and peripheral nerve tracts put an end to the horror of spinal cord injury, but it would also be significant in dealing with other neurological disorders, such as stroke, multiple sclerosis, and head injury.

Peripheral nerves, when injured, normally regenerate and form both motor and sensory functional connections. Regeneration of the goldfish spinal cord has been accomplished, and Soviet scientists have reported the successful regeneration of the rat spinal cord. As a result of these developments, and of the interest of the U.S. Congress in spinal cord injury, an Ad Hoc Subcommittee on Growth and Regeneration in the Central Nervous System was established by the National Advisory Neurological and Communicative Disorders and Stroke Council in 1973. Its mission was to evaluate the current status of regeneration research and to identify those areas where potentially significant advances might be expected.

The Ad Hoc Subcommittee implemented its task through four workshops and six solicited manuscripts to provide relevant background information. Fifty of the top experts in the field of regeneration participated in preparing the report which was submitted to the Council in March 1975. This information on high priority research areas, training, and planning and coordination was thought to be of sufficient importance to warrant publication in its entirety in the September 1975 issue of Experimental Neurology. As a result, the full report is now in the hands of almost all of the leaders in this research area and is expected to stimulate research in consonnance with its recommendations.

Progress in this area is painfully slow. However, it has now been established that two kinds of regeneration occur following injury to the central nervous system: (1) terminal regeneration, in which an injured nerve regrows its severed nerve process and (2) collateral regeneration, in which normal intact nerve fibers in the region of denervated nerve cells sprout additional branches which reinnervate the adjacent denervated cells and may function in place of the lost neurons.

Another important development is the discovery of a nerve growth factor which is capable of enhancing the growth of nerve cells and their connections. In a recent application of this new knowledge, an NINCDS grantee Stanley M. Crain, Yeshiva University, observed that axons of nerve growth factor-enhanced fetal mouse dorsal root ganglion cells can not only establish characteristic synaptic network function in dorsal roots of attached spinal cord tissue culture, but, also some of the axons may grow through the cord tissue in these cultures and make similar function synaptic connections with specific types of "target" neurons in localized zones within nearby medulla explants. These findings may provide the basis for a significant new model system and make it possible to analyze the mechanisms underlying the formation and development of specific synaptic connections in the mammalian central nervous system. Experimental manipulation of these programmed neuronal interactions in the laboratory may also shed light on the more general problem of cell recognition leading to joint function between cells of different types.

Numerous other similarly technical experiments are being conducted at grantee institutions and at the Institute's Bethesda laboratories. To the scientist, and most especially to the person with paraplegia, the process of acquiring new knowledge appears laborious and painfully slow. However, the history of science shows clearly that improvements in the treatment of disorders are largely dependent on carefully thought out basic approaches to acquiring "missing information." In the interim, through the NINCDS network of Acute Spinal Cord Injury Clinical Research Centers, new clinical knowledge is thoroughly evaluated and rapidly disseminated.

A good example of the evolutionary nature of basic research is the work that was done by Dr. William F. Windle, while he was on the Institute staff. 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 they report 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.

In order to evaluate these results, the NINCDS, through the US/USSR Health Exchange Program, Office of International Health, Department of Health, Education, and Welfare, last year proposed a conference with the Soviet scientists at which their findings could be discussed with US scientists in the field of cord injury research. Preliminary arrangements for this interchange have been initiated, and it is hoped that final arrangements will be completed in 1976.

OFFICE OF HUMAN DEVELOPMENT

Rehabilitation Services Administration

Spinal Cord Injury

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. This year, a national coordinating center for the retrieval and analysis of valuable data has been established, as part of a model system.

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 60 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.

OFFICE OF HUMAN DEVELOPMENT

Rehabilitation Services Administration

SPINAL CORD INJURY

Fiscal Year	1973	1974	1975	1976 Estimate	1977 Estimate
Service Projects	-	-	-	$1,000,000	$2,100,000
Research and Demonstrations	$2,100,000	$2,100,000	$1,500,000	1,500,000	250,000
Rehabilitation Research and Training Centers	689,000	716,000	1,200,000	1,200,000	1,054,000
Special Foreign Currency Program	-	-	110,000	150,000	200,000
Total, Human Development.....	$2,789,000	$2,816,000	$2,810,000	$3,850,000	$3,604,000

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.

There are many types of strokes, but in a large number of cases, it is impractical or impossible for the physician, in preparing the death certificate, to ascertain the specific cause of the stroke. The following table, based on figures collected by the National Center for Health Statistics, shows the principal categories used by physicians in certifying stroke deaths.

U. S. Stroke Mortality - 1973

Acute but ill-defined cerebrovascular disease	67,730
Generalized ischemic cerebrovascular disease	39,261
Subarachnoid hemorrhage	9,191
Cerebral hemorrhage	33,909
Occlusion of precerebral arteries	3,177
Cerebral thrombosis	56,648
Cerebral embolism	967
Transient cerebral ischemia (minor strokes)	61
Other and ill-defined cerebrovascular diseases	3,369
	214,313 total

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 nonhospital 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 of Health, Education, and Welfare's activities in cerebrovascular disease are conducted by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) with the cooperation of the National Heart and Lung Institute (NHLI) of the National Institutes of Health (NIH) and by the Social and Rehabilitation Service (SRS). Stroke research is a major area of NINCDS responsibility and has been given a high priority in planning and development. Rehabilitation is the responsibility of SRS.

Obligations for Programs in Stroke (Cerebrovascular Disease)

	1973	1974	1975	1976 estimate	1977 estimate
National Institutes of Health:					
National Institute of Neurological and Communicative Disorders and Stroke	$6,983,000	$8,086,000	$9,788,000	$10,017,000	$10,333,000
National Heart and Lung Institute	2,277,000	3,662,000	3,733,000	4,000,000	3,700,000
Total	9,260,000	11,748,000	13,521,000	14,017,000	14,033,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological and Communicative Disorders 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) has been 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 loss 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 NINCDS 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 NINCDS stroke program. In Fiscal Year 1975, Institute support for research in stroke reached a level of approximately 9.8 million, representing 36 research project grants, 15 clinical research centers, 10 acute care research units, 7 research contracts, and approximately 20 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 conducted at the Institute in Bethesda, includes studies of nonacute cerebrovascular disease in young patients (up to 40), and a series of animal studies aimed at possible salvage and preservation of brain tissue after a stroke. Also, the Institute recently established a Section on Head Injury and Stroke which has been conducting, through contracts, a multi-institutional study of the hospital frequency and characteristics of transient ischemic attacks (little strokes). This study, which will provide data on approximately 1,000 patients, has been completed, and will be reported on in 1976.

Clinical Research Centers

Cerebrovascular clinical research centers 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. The units 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 using 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 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 NINCDS 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.

NINCDS has sponsored several large cooperative studies in cerebrovascular disease. The largest, which has been in progress since 1958, has produced a wealth of data on the treatment of intracranial aneurysms, and subarachnoid hemorrhage. This year, the coordinating center for the study at the University of Iowa has reported favorable results with two antifibrinolytic (clotting) agents, epsilon-aminocaproic acid, and tranexamic acid. Over a 20-month period, the drugs were given to 502 patients in 13 institutions following ruptured intracranial aneurysms. Mortality at the end of 14 days was 11.6 percent; rebleed rate 12.7 percent. These percentages compare very favorably with the rates for an earlier group of patients in the study for whom the treatment was confined to regulated bedrest: the corresponding rates were both around 20 percent.

Other Groups Working in the Stroke Field

The National Heart and Lung Institute (NHLI) also supports 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. 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 over 15,000 stroke patients in its hospitals in Fiscal Year 1975.

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 1974, 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 radiopaque 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 or are in limited use, including injection or inhalation 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 axial tomography, has been hailed by an NINCDS 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 poses no danger or discomfort to the patient.

A substantial number of EMI scanners are now in operation in U.S. medical centers, and a major effort is under way to refine and improve the method. Whole body scanners are under development, and the equipment is being designed to work at higher speeds, both to enhance the screening possibilities, and also to surmount problems caused by body movements, i.e. breathing and heartbeat. Most of the institutions housing stroke research centers now have the equipment.

Several scanners are in operation at the National Institutes of Health, and NINCDS radiologists are also working with the Georgetown University Radiology Department in Washington, D.C. in spinal cord studies. A new contrast medium, Metrizamide, is being tried, and methods are being developed for scanning the spinal cord in coronal and sagittal planes. Research projects using one of the scanners at the NIH Clinical Center include studies of changes in absorption coefficients in the basal ganglia, studies of calcification in this area of the brain, and studies of the orbit (eye socket). This area has always been extremely difficult to reach with conventional X-ray.

Experiments with one of the other diagnostic techniques mentioned above, gas inhalation, have produced data this year of interest to those pondering the question, "Does the damaged brain try harder?" Essentially, the technique permits the regional monitoring of cerebral blood flow by having the patient inhale a radioactively labeled inert gas, Xenon, and then tracing its course through the brain with a highly sensitive radiation counting camera. The scientists, working in one of the NINCDS supported stroke research centers at the University of Alabama, first measured cerebral blood flow (CBF) in a group of normal young men in the resting state, during movement of one hand, and during spontaneous speech. The measurements revealed significant CBF increases in the brain regions classically associated with these functions. Then the same tests were performed in patients with hemiparesis (paralysis on one side) and aphasia (speech paralysis). Two surprising findings appeared: in some patients, the effort to carry out a function which is impossible or very difficult, e.g., to move the hand in the presence of hemiplegia may cause a decrease in cerebral blood flow in the region of that function or in the whole brain. However, in some patients recovering from aphasia due to a left hemisphere lesion, substantial increases in CBF are seen to occur in the right hemisphere during the effort to use word symbols. One might theorize from this that a process exists whereby the undamaged side of the brain can take over at least some of the function lost by the other side.

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.

During the year, Institute grantees reported numerous projects, including work on development of better animal models for experimental stroke surgery; a new ventricular catheter which will be able to record, in addition to intracranial pressure, oxygen at various levels of the cortex, and local blood flow; and a large number of studies aimed at better assessing cell damage following strokes.

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.

Interest has mounted in the past several years in the possible role of neurotransmitters in stroke. These substances provide electrochemical mechanisms for transmitting impulses or inhibitory or excitatory influences from one nerve to another, or to a target muscle or organ. Several neurotransmitters are believed to "leak" out of the nerve cells following a stroke or other injury to the brain or central nervous system, setting up a vicious circle in which the problem is further aggravated. Among the theories proposed are that the neurotransmitter molecules may flood receptor sites, causing hyperpolarization or depolarization and consequent interference with normal transmission, and that some of them may act on local blood vessels, causing further constriction, deprivation of blood supply, and spasm. Whatever the answer turns out to be, it has been established in experimental animals that neurotransmitter levels start to fluctuate greatly immediately following an induced stroke.

In one study with gerbils, brain cell dopamine levels fell to less than half of normal following tieing of a major (carotid) artery. Institute scientists and grantees are now focusing on such questions as which particular brain cells are involved; whether similar changes occur in the brains of humans suffering strokes; precisely how the dopamine may affect structures beyond the synapse; whether there might be some treatment benefit in using drugs to block dopaminergic receptor cells soon after strokes; and whether longer term stroke survivors suffer from inadequate dopaminergic stimulation, which might be treated with drugs like L-Dopa and apomorphine. They suggest that perhaps some day strokes, like Parkinson's disease, will be treated with drugs designed to modify the levels or actions of neurotransmitters.

Efforts continue to test and improve existing drug therapy in stroke, but progress has been slow and difficult. For example, two studies reported this year of trials with vasodilators, one with cyclandelate, the other with betahistidine hydrochloride, showed that they were no better than placebos. The accounts demonstrate the enormous difficulty investigators face in finding drugs which will clearly benefit patients who have suffered brain damage.

Another possible research approach to drug treatment in stroke has come from the NIH. An NINCDS 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 NINCDS 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 supports a program of acute care research units in 10 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.

Race and Environment

For many years, differences in morbidity and mortality from stroke among different racial groups and the same racial groups in different environments has interested epidemiologists. Several reports were published this year of studies of cerebral vessels obtained from autopsies of American Negroes, Caucasians, and Nigerian Africans, all living in urban areas. The scientists found that the American (Washington, D.C.) Negroes had more than three times as much cerebral vascular cholesterol as the Nigerians (in Ibadan), with the American Caucasians (Minneapolis) falling roughly halfway between. The high cholesterol levels in the cerebral vessels in American blacks suggests a correlation with the greater severity and extent of cerebral atherosclerosis in this group.

The scientists also studied trace metal content of the cerebral vessels in the same three groups. Trace metals measured included calcium, manganese, zinc, magnesium, copper, and iron. American Negroes showed the greatest amounts of calcium, zinc, and copper, while the Minnesota Caucasians showed the highest levels of magnesium. The Nigerians had the least copper and magnesium, but the highest iron levels. The conclusions were that a relationship may exist between the high concentrations of copper and magnesium and cerebral atherosclerosis, and that the low levels of these elements in Nigerians may be protective.

Decline in Stroke Incidence Rates

Reports this year from the Institute-supported Mayo Foundation Cerebrovascular Clinical Research Center present some rather striking statistics on declining incidence rates. Scientists there have found that the incidence rate for all strokes, and cerebral infarction in particular, has decreased in each 5-year interval since 1955 in Rochester, Minnesota. During the full 25 years of study of this population, there has been a decrease from the earliest to the latest 5-year period of 32 percent for all strokes in women, and 20 percent in men. They suggest that this reflects improvement in treatment, particularly the increasing use of effective blood pressure lowering drugs.

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 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 under way between the NINCDS and clinical scientists in India regarding a possible collaborative stroke study in that country.

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 the 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 supporting projects related to SIDS involve the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the National Heart and Lung Institute (NHLI), and the National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD) of the National Institutes of Health; Office for Maternal and Child Health, Bureau of Community Health Services, 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

	1973	1974	1975	1976 Estimated	1977 Estimated
National Institutes of Health:					
National Institute of Child Health and Human Development	$4,106,000	$5,300,000*	$6,322,000	$6,830,000	$6,400,000
National Institute of Neurological and Communicative Disorders and Stroke	105,000	---	35,000	35,000	---
National Heart and Lung Institute	---	20,000	25,000	30,000	30,000
National Institute of Arthritis, Metabolism, and Digestive Diseases	---	---	----	35,000	35,000
Health Services Administration: Bureau of Community Health Services Maternal and Child Health	9,800	114,000	2,000,000	2,500,000	---
Health Resources Administration: National Center for Health Statistics	11,000	1,000	2,000	2,000	3,000
Alcohol, Drug Abuse and Mental Health Administration: National Institute of Mental Health	---	---	65,000	65,000	---
Total	$4,231,800	$5,435,000*	$8,449,000	$9,497,000	$6,468,000

*Includes restoration of 1973 impounded funds in the amount of $616,000.

Prepared December 1975

NATIONAL INSTITUTES OF HEALTH

National Institute of Child Health and Human Development

The sudden infant death syndrome (SIDS) is defined as the sudden death of any infant or young child which is unexpected by history and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death. Other terms frequently used to describe the syndrome include crib death, cot death, sudden unexplained death, and sudden death in infancy.

SIDS strikes without warning and usually during a sleep period. The SIDS victim has usually been well cared for and considered to have been in good general health and eating well before death. A number of infants have been seen by a physician for a routine checkup within 24 to 48 hours before death, during which no major health problems were found. 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 about one-half of the cases there is a history of a slight upper respiratory infection which is usually of such a minor degree that medical advice was not sought. 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 public health problem. Its age distribution is impressive and considered to be the syndrome's single most characteristic demographic feature. The peak incidence is consistently found the world over to be between the 2nd and 4th months of life. SIDS occurs more frequently in males than in females in a ratio of 3:2. The incidence is higher in non-white than in white babies, in one of twins as compared to single born babies, in families of lower socioeconomic status, in low birth-weight infants and particularly in premature infants who had gestational ages between 34 and 35 weeks, and in babies who had recent upper respiratory infections. The frequency of SIDS deaths in the United States is higher during the cold weather months, particularly between November and March, and in urban areas as compared to rural areas. SIDS deaths occur more frequently between 12 midnight and 8:00 a.m. than during other periods of the 24 hours.

Many causes have been offered to explain these deaths including neurophysiologic, cardiorespiratory, metabolic, endocrine, and immunologic disturbances, and infections. However, to date no single cause has been shown to be responsible for these deaths. Why these infants die so suddenly, quietly, and unexpectedly is still unknown.

The Sudden Infant Death Syndrome Act of 1974

The Sudden Infant Death Act of 1974 (P.L. 93-270) 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. Specific reports to Congress pertaining to progress of programs concerned with SIDS are required yearly for the period ending June 30, 1977.

The NICHD has been designated as the lead agency for P.L. 93-270 and has been given responsibility for coordination and implementation of the law. The National Institutes of Health has selected SIDS for FY 76 tracking through the NIH Operational Planning System. In addition, SIDS has been incorporated into the DHEW Child Health Task Force Operational Plan for FY 1976.

The DHEW has established an interdepartmental committee to coordinate Federal efforts in SIDS. It is chaired by an official of the NICHD and has representation from the National Institute of Neurological and Communicative Disorders 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 is included as appropriate.

Research Objectives in SIDS

During 1975, the NICHD continued to expand its research efforts on the sudden infant death syndrome. Program objectives include:

1. To increase understanding of underlying mechanisms of the syndrome.

2. To discover its probable cause or causes.

3. To identify infants at risk of becoming victims and to explore preventive approaches.

4. To elucidate the impact of a sudden and unexpected infant death on the subsequent behavior of parents and siblings.

5. To stimulate scientists to direct investigative efforts toward the solution of this complex problem.

6. 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 SIDS Research Planning Workshops to consider the nature and scope of this problem and 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 of the eleven Workshops has been published or is currently in press.

In February 1974, the NCIHD 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 by sharing them with the scientific community and public. The subjects of the two lectures given in 1975 were: Cardiopulmonary Patterns During Quiet and Active Sleep States in the Fetus and Infant: Implications for SIDS; and Respiratory Control Mechanism in the Neonate as Related to SIDS.

In June 1975, the NICHD held its first SIDS Research Reporting Workshop. The purposes of this workshop, attended by approximately 70 NIH supported investigators and staff working on the problems of SIDS, were: to assess the current status of SIDS research; to identify accomplishments to date; to evaluate progress; to facilitate the early dissemination of findings and the exchange of information among scientists, concerned citizens, and representatives of SIDS parent organizations; and to identify areas in which additional investigative efforts are needed. It is planned to hold future SIDS research reporting workshops biennially.

NICHD Research Programs

The NICHD has developed its SIDS research around seven areas:

1. Abnormal sleep patterns related to breathing, circulation, and other functions essential for 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 1975 there were 130 ongoing research projects pertaining to SIDS. They included 33 grants and contracts for research specifically concerned with SIDS, and 97 grants and contracts for related studies. FY 1975 support approximated $6.3 million compared with $5.3 million in FY 1974. Funding for FY 1976 will approximate $6.3 million.

As a result of intensive investigations of SIDS between 1972 and 1975 by NICHD-supported investigators, there is now a growing body of evidence that the victims of crib death are not completely normal and healthy and their deaths not as inexplicable as was once thought. It appears that these infants have subtle physiological defects of a neurological, cardio-respiratory and/or metabolic nature. It is also evident now that the pathogenesis of the syndrome is not through a single mechanism as previously believed. Instead, a number of developmental, environmental, and pathologic factors appear to be involved which under a complex set of circumstances interact in such a way as to set up rapidly a sequence of events that produces a sudden, unexplained, and unexpected infant death.

An important advancement in our understanding of a possible pathophysiologic mechanism of SIDS comes from the investigations of Richard Naeye of the Milton S. Hershey Medical Center of Pennsylvania State University College of Medicine who found that the tissues of crib death victims have certain characteristics resembling those seen in infants known to have had chronically low concentrations of oxygen in their blood. The characteristics include the presence of considerably more muscle about the small arteries of the lungs than is seen in infants not subject to oxygen deficiencies; synthesis of red blood cells in the liver and not just in the bone marrow as in normal infants; and prolonged retention of brown fat around the adrenal glands. In normal infants brown fat is gradually replaced by white fat during the first year of life. In crib death victims and also in infants who died from congenital heart conditions and were therefore receiving inadequate oxygen, the loss of brown fat was greatly slowed in comparison to that in infants who had died suddenly in accidents or from acute infections.

These data provide the first evidence that SIDS victims have been subjected to some type of chronic stress for varying periods of time before death. Confirmation of the synthesis of red blood cells and brown fat findings by Maria Valdes Dapena of the St. Christopher's Hospital for Children in Philadelphia is viewed as additional evidence of exposure of SIDS babies to prolonged periods of chronic stress and hypoxia.

In 1974 Alfred Steinschneider of the Upstate Medical Center of the State University of New York demonstrated that in infants periodic cessation of breathing for 10 seconds or longer (apnea) during sleep and associated changes in heart rate are part of a normal developmental pattern that occurs during the early months of life. He has now shown 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. Several of the infants observed to have abnormal breathing during sleep (sleep apnea) have died from SIDS after discharge from the hospital. These observations are important because frequent periods of apnea can affect the supply of oxygen to body tissues and may unduly stress body function.

Elliott Weitzman and Ann Cornwell of the Montefiore Hospital Medical Center in New York City are studying babies who have been seen in an emergency room because of a prolonged apnea episode and considered to be a "near miss SIDS." Preliminary analysis of data obtained on 4 "near miss" infants and compared to 3 normal, age-matched infants reveals a different pattern of sleep and a larger number of prolonged apneic episodes.

William Dement and Christian Guilleminault of Stanford University School of Medicine in California have identified three kinds of apnea in premature and "near miss" infants. These include: central or diaphragmatic apneas which involve no movements of the respiratory muscles of the abdomen and chest; upper airway apnea where the muscles move but there is no air exchange; and mixed apnea in which a period of upper airway follows one of central apnea. These investigators have observed that a slowing of the heart rate occurs in infants during all three types of apnea. This apnea is more severe during episodes of the upper airway type and the mixed type. In addition a greater loss of oxygen from the blood and more frequent abnormalities in the rhythm of heart beats were observed.

In other studies one investigator has observed abnormalities in the area of the brain which controls respiratory rhythm and function. Another scientist, studying enzymes present in the brain stem which are involved in the control of substances related to the transmission of nerve impulses, has found that in some cases a specific enzyme appears to be lacking or is very low in concentration in the brain-stems of SIDS victims. More data are required to confirm this. Other scientists are investigating reflexes which control breathing and swallowing. They have observed in lambs that water, sugar water, or cow's milk in contact with receptors in the larynx caused sustained apnea whereas salt solution or colostrum (the first mother's milk) did not.

With the support of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), Dr. Richard Naeye of the Hershey Medical Center, the Pennsylvania State University, is conducting an analysis of all the deaths of children within the framework of the Collaborative Perinatal Project. About 125 children with SIDS have been identified, and the prospectively collected data from the mother's pregnancy, labor and delivery, as well as the neonatal data on each of the victims, is being analyzed in order to determine relationships between these data and the occurrence of the syndrome. Preliminary analysis shows that SIDS babies had more problems in the neonatal period than their controls.

The National Heart and Lung Institute is investigating the relationship between cardiac abnormalities and SIDS under Dr. Stephen Epstein, Chief of the Cardiology Branch, and Dr. Barry Maron, senior investigator of the Branch. It has been found that prolongation of QT interval (a finding associated with sudden death in adults, children and infants) was present in about 25 percent of 42 families in which an infant died of SIDS.

The National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD) is supporting research by Dr. Henry Lardy, of the Institute for Enzyme Research at the University of Wisconsin, as part of an overall investigation of enzyme action. The investigators are studying correlation of SIDS with abnormalities in the ability of the children to synthesize glucose. The activity of certain gluconeogenic enzymes of livers from SIDS victims was compared with those from infants dying of other causes. It was found that activity of a particular enzyme required for gluconeogenesis was considerably lower in SIDS infants than in other infants. In addition, a high percentage of the SIDS victims had an hepatic function of this enzyme that was

defective in its response to certain metals. While these preliminary findings are stimulating considerable interest, the investigators still have no evidence that hypoglycemia is a cause of death in SIDS.

NICHD Information Program

The Institute has a number of publications available for distribution to the scientific community and general public. These 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

SIDS: Selected Annotated Bibliography, 1972-1974

Research Planning Workshop on the Sudden Infant Death Syndrome (An Overview)

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

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 (in press)

SIDS Research Planning Workshop: Approaches to Establishing Case Registers and Clinical Trials (in press)

SIDS Research Planning Workshop: Impact on Parents and Siblings (in press)

Crib Death: Some Promising Leads But No Solution Yet. Science, 189:367, August 1, 1975. (Reprinted with permission of Science.)

Sudden Unexpected Death In Infants. National Library of Medicine Literature Search.

Reaction to Infant Death by Family and Social and Legal Institutions. National Library of Medicine Literature Search.

Attitudes Toward Death. National Library of Medicine Literature Search.

Development of Upper Respiratory Anatomy and Function: Implications for Sudden Infant Death Syndrome.

The Sudden Infant Death Syndrome Act of 1974: Approaches to Implementation (in press)

The Role of Cardio-Respiratory Electronic Monitoring of Young Infants in the Home Environment (in press)

Research Perspectives in the Sudden Infant Death Syndrome 1975: Proceedings of a Research Reporting Workshop (in press)

HEALTH SERVICES ADMINISTRATION

Bureau of Community Health Services, Office for Maternal and Child Health

The activities of the Bureau of Community Health Services, Office for Maternal and Child Health, in the first twelve months following the signing of the SIDS Act of 1974, largely focused on the development of an implementation plan, writing and publication of regulations, preparation and distribution of program guidelines, and initiation of recruitment and counseling projects. Activities also focused on completion of the film "After Our Baby Died", distribution of the film, and a variety of publications on SIDS.

Regulations for the SIDS grant program were developed and published as Notice of Proposed Rulemaking in the Federal Register on March 5, 1975, with final regulations for project grants for Sudden Infant Death Syndrome Information and Counseling becoming effective on June 6, 1975.

Interim guidelines based on the proposed regulations were prepared in April 1975 and distributed to prospective grantees and other interested parties. Application materials were mailed to 170 potential applicants on April 1, 1975. The publication of program regulations late in the fiscal year and the President's recission message that delayed the release of funds until March 1975 precluded earlier distribution of this material.

Awards were made to 24 project applications on June 30, 1975. The projects are located in 21 States and in 9 of the 10 H.E.W. regions. The 24 supported projects cover a population base of 81,918,838. The number of infant deaths caused by the Sudden Infant Death Syndrome (SIDS) in the project areas is anticipated to be approximately 3,347 per year. This figure is about half the expected annual total of SIDS deaths for the United States.

Applications were approved for funding on the basis of criteria established in the program regulations and guidelines. Identified in their project plan was a systematic approach to the local management of problems associated with SIDS, utilizing existing community resources and establishing important linkages between involved community agencies. Minimal acceptable standards for handling SIDS include:

(1) The availability of autopsies performed by qualified pathologists for all infants who die suddenly and unexpectedly, (2) The term "Sudden Infant Death Syndrome" to be designated as the cause of death on death certificates, when appropriate, (3) The notification of families about the results of the autopsies without undue delay, preferably within 24-48 hours, (4) Follow-up information about SIDS and the characteristic grief reaction as well as appropriate counseling be provided.

In addition to the above services to families, all projects are required to initiate local educational activities for health professionals, public safety officials and others involved in the program, and to identify mental health back-up services for consultation to project staff and for family referrals.

Educational and Consultation Activities of the SIDS Program

Two statewide conferences were supported with fiscal year 1975 funds, designed to increase the awareness of health professionals to problems encountered by parents upon the death of an infant and for discussion of the meaningful role the nurse, physician, or social worker can play in assisting the family through the grief period. A one-day symposium was conducted in May 1975 at the Baylor University Medical Center in Texas for 109 participants. In New Jersey, two conferences were conducted in November 1975 attended by approximately 300 physicians, nurses, social workers and representatives of SIDS voluntary organizations through the State.

In November 1975 a national meeting of pathologists representing the 24 SIDS projects, selected invitees with expertise in associated areas of forensic pathology and toxicology, and representatives of national professional associations of pathologists was convened in Santa Fe, New Mexico. Recommendations were made at this working conference related to standardized death investigation and autopsy protocol as well as the development and maintenance of a SIDS data registry.

The film, "After Our Baby Died" was completed and is being distributed by the Bureau under contractual arrangements to schools of medicine, nursing, hospitals, health agencies and professional associations. Initial response has been unusually positive and resulted in the need to double the original order for 50 prints. As of January 1, 1976, the film has been shown 1,117 times to a reported audience of approximately 14,800 persons, and is also being used by the 24 SIDS projects in their professional educational programs. The film can be purchased through Audio-visual Center (GSA) for $84.00 per copy. To date, 35 prints have been sold to State film libraries, chapters of the National Foundation for Sudden Infant Death, Inc., and the International Guild for Infant Survival.

Two other films are currently in production. One film, which explores the normal grief, self-blame and guilt experienced by SIDS parents, is scripted for families as the primary audience. The second film is being developed with the cooperation of the International Association of Chiefs of Police and the American Academy for Professional Law Enforcement, and will be used as a training film to acquaint police officers with SIDS and to outline their responsibilities in dealing with SIDS parents.

A number of publications on SIDS is being distributed to the general public and to specific audiences as nurses, pediatricians, obstetricians, pathologists, social workers, police and others. The total number distributed to date is 174,638.

HEALTH RESOURCES ADMINISTRATION

National Center for Health Statistics

NCHS instituted a special code in the International Classification of Diseases (adapted) for SIDS beginning with 1973. Table plans have been completed for multiple cause of death tabulations concerning SIDS.

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.

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